Screening immigrants for latent tuberculosis

A cost-effectiveness analysis in a Norwegian setting

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Master thesis

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Abstract

Background: Tuberculosis (TB) is an infectious disease caused by a bacterial infection. In Norway, screening immigrants for and treating latent TB infection (LTBI) is done to prevent active TB. LTBI, unlike active TB, does not cause symptoms but may cause progression (reactivation) to active TB later. The current screening strategy is a two-step strategy screening with tuberculin skin test (TST) and interferon gamma release assays (IGRA) when the TST is positive on immigrants from countries with a high prevalence of TB. A new screening strategy for LTBI where only IGRA is used will likely be introduced. Two other options, no LTBI-screening or screening only those with risk factors for reactivation may be considered as well because of potentially reduced costs. Before the new strategy is implemented the options for screening should be evaluated.

Aim: The study was designed to compare the cost-effectiveness of four different screening strategies for LTBI in immigrants in Norway using cost-effectiveness analysis (CEA).The strategies were: (1) No screening for LTBI, (2) screening only people with risk factors for reactivation with IGRA, (3) screening all immigrants with TST and IGRA, and (4) screening all immigrants with IGRA only.

Methods: A combined decision tree and Markov-model was developed where the outcome was avoided cases of active TB. The model was partially probabilistic. Costs were considered from a health budget perspective. Both deterministic and probabilistic sensitivity analyses (PSA) were conducted. Expected value of perfect information was estimated to indicate the potential gains from further research.

Results: The results of the model indicate that the strategy combining TST and IGRA is not cost-effective at any willingness-to-pay (WTP) threshold. The three other screening-strategies were cost-effective at different thresholds of WTP. Screening all immigrants with IGRA was cost-effective at a WTP above NOK 222 000. Screening only immigrants with risk factors was cost-effective between a WTP of NOK 24 000 and NOK 222 000, while no LTBI-screening was cost-effective when WTP is below NOK 24 000.

Conclusion: Going from the two-step model to IGRA would be cost-effective if the WTP is above NOK 222 000 per avoided case of active TB. No LTBI-screening or screening only immigrants with risk factors should be considered if the WTP is below NOK 222 000.

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Acronyms

BCG	Bacillus Calmette-Guérin
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CUA	Cost-utility analysis
DOT	Directly observed therapy
DRG	Diagnosis related group
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect parameter information
FFS	Fee for service
HIV	Human immunodeficiency virus
ICER	Incremental cost-effectiveness ratio
IGRA	Interferon gamma release assay
LTBI	Latent tuberculosis infection
MDR-TB	Multi-drug-resistant tuberculosis
MSIS	Norwegian Surveillance System for Communicable Diseases
NIPH	Norwegian Institute of Public Health
NPV	Negative predictive value
OUS	Oslo University Hospital
PPD	Purified protein derivative
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
QALY	Quality Adjusted Life Years
QFT-GIT	QuantiFERON-TB Gold In-Tube
RCT	Randomized controlled trial
TB	Tuberculosis
TST	Tuberculin skin test
VAT	Value added tax
WHO	World Health Organization
WTP	Willingness-to-pay
XDR-TB	Extensively drug-resistant tuberculosis

1 Introduction

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis* (Merck, 2009*)*. Even if it is a preventable and treatable disease there were around 8.6 million new TB cases and 1.3 million deaths worldwide in 2012 (WHO, 2013). It is the second leading cause of death from infectious disease after the human immunodeficiency virus (HIV) (WHO, 2013).

In Norway there have been between 300 and 400 cases of tuberculosis per year the last decade. In Figure 1 we see that the number of cases reported to the National Institute of Public Health (NIPH) declined from 1978 to the mid-nineties. At that time the number of reported cases started to increase again, even when the reported cases in the Norwegian-born population kept on decreasing. The reason is that more TB-cases in Norway now occur in the foreign born population.

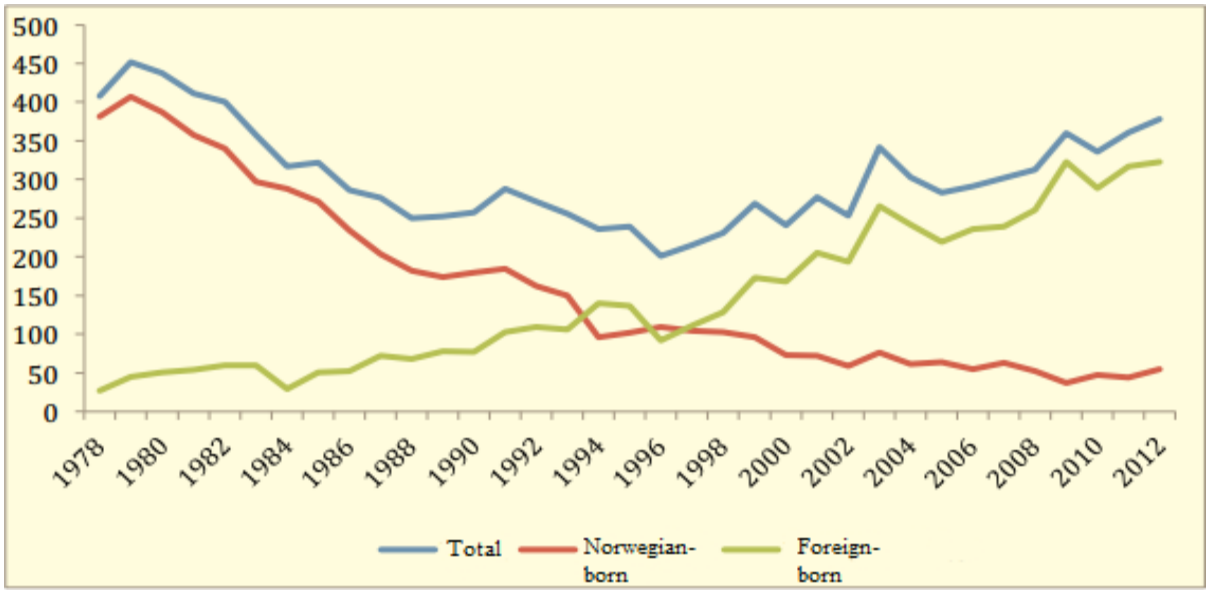

Figure 1 Cases of tuberculosis from 1978 to 2012 reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) (Arnesen et al., 2013)

Early detection and treatment of tuberculosis is not only important to stop transmission to other individuals, but it can also help to halt the increase of cases that are resistant to medication (NIPH, 2013), which require longer and more expensive treatment. One possibility is to screen for and treat latent TB infection (LTBI). LTBI occurs when the initial infection is halted and does not turn into active disease. Because a person with LTBI is at risk

of developing active TB later (reactivation), treating LTBI can reduce the amount of TB cases developed in the future.

In Norway screening for and treating both active TB and LTBI is currently being done on immigrants from countries with a high prevalence of TB. LTBI-screening is done with a two-step strategy, where a tuberculin skin test (TST) is taken first, and an interferon gamma release assay-test (IGRA) is taken if the TST is positive. A new strategy in which immigrants are tested only with IGRA will likely be introduced in the near future. Before the new strategy is implemented the options for screening should be evaluated.

It could be interesting to consider strategies which a priori seem as though they may reduce costs. Because resources are scarce screening involves a tradeoff. Resources spent on LTBI cannot be used on other health interventions, so it is important to ensure that the resources are used in a way that ensures as much benefit as possible. Possible strategies that could reduce costs are screening only immigrants at high risk for reactivation and not screening for LTBI at all. Intuitively, screening only immigrants at risk for reactivation could decrease costs without substantially increasing the amount of cases of active TB. Not screening for LTBI could also be done. In that case it would be necessary to treat more reactivated cases in the future. Whether this saves costs or not is difficult to know a priori.

This study was designed to identify which screening strategies for LTBI would be cost-effective in Norway, by comparing the four different strategies mentioned above: (1) No screening for LTBI, (2) screening only people with risk factors for reactivation with IGRA, (3) screening with TST and IGRA, and (4) screening all immigrants with IGRA only. The comparison was done using cost-effectiveness analysis (CEA). A benefit of the study will also be that it provides rough estimates of the costs of screening and treating latent and active tuberculosis in Norway.

Including the introduction, the thesis is divided into eight chapters. The second chapter provides information about TB and screening. The third chapter provides some theoretical information about health economic evaluation. The fourth chapter states the research question. The fifth chapter describes the methods used in this study. The sixth chapter shows the results of the model and sensitivity analyses. The seventh chapter consists of a discussion of the results and strengths and limitations of the study. The eighth and final chapter provides the conclusion.

2 Background

2.1 Tuberculosis

There are different types of TB. TB can be pulmonary, laryngeal, urogenital and renal. It is also possible to have tuberculous meningitis and tuberculosis in the lymph nodes, but TB in the lungs (pulmonary TB) is the most common type (WHO, 2013). About two thirds of tuberculosis cases reported in Norway in 2012 were cases of pulmonary TB (Arnesen et al., 2013).

The symptoms of pulmonary TB can be prolonged cough with sputum, fever, night sweats, and feeling unwell. The main symptom is probably cough with sputum (NIPH, 2013). One problem with this type of symptoms is that they are unspecific and it can be difficult to suspect TB on the basis of them. It is also possible to have no symptoms, at least in early phases of the disease (Merck, 2009; NIPH, 2013). These factors can contribute to delay in seeking help and can lead to transmission of the bacteria to other people (WHO, 2014). The symptoms of TB in other organs than the lungs (extra-pulmonary TB) vary depending on where the TB is located, and these symptoms will not be pursued further here.

The main route of infection by TB is by inhaling airborne droplets expelled from people with pulmonary TB. Although other rare ways of becoming infected exist as well (Merck, 2009), pulmonary TB is generally considered the only infectious type of TB. To be able to transmit the disease, a sufficient amount of bacteria is required in the sputum. When the bacteria are inhaled by another person, they are transmitted down to the alveolar surfaces of the lungs where they breed and further spread (Merck, 2009).

Whenever the droplets are expelled out into a room and reach a surface it is hard to make them airborne again as inhalable particles. Because of that, once the droplets reach a surface their ability to spread the infection is weakened (Merck, 2009). The risk of infection may increase with recurring contacts with an infected and untreated individual, or by staying in the same poorly ventilated room for a longer period (Merck, 2009). WHO estimates that approximately 10-15 people get infected for every person ill of TB (WHO, 2014), but once treatment is started the contagiousness of the disease decreases rapidly (Merck, 2009).

In most people the initial infection is stopped or eliminated by host defenses, which means the infection will remain latent (latent tuberculosis infection, LTBI) (Pai et al., 2014). This happens in about 95% of TB-infections (Merck, 2009), so in most cases people do not develop active TB (pulmonary or extra-pulmonary) on the onset. People with LTBI are asymptomatic and cannot infect others (Pai et al., 2014), but the bacilli may reactivate and cause active TB later. About 1/3 of the world's population is estimated to be infected with TB, and most of these are cases of LTBI (Merck, 2009). 1/3 of the world's population then has the potential for reactivation.

The probability that the infection will cause reactivation varies from sub-group to sub-group, and is a debated number (Pareek et al., 2011). Some groups are considered especially at risk for reactivation, such as the immunosuppressed (young children and HIV-infected) and people recently infected. HIV-infected also have a higher mortality rate once they develop active TB (WHO, 2013).

One subject that has been in focus lately is the fact that the prevalence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) has been on the increase (Merck, 2009). MDR-TB is defined as TB that is resistant to the first-line drugs isoniazid and rifampicin. XDR-TB is defined as resistance to both isoniazid and rifampicin, and in addition other second-line drugs (NIPH, 2013). These types of TB are harder and more expensive to treat, and the treatment of TB has been focused on getting people to complete treatment to avoid development of MDR bacteria.

2.2 Diagnosis

Active TB is often suspected on the basis of symptoms, and further inquiries are made with chest x-rays (Merck, 2009). Changes in the findings on chest x-rays are considered the most important indication of pulmonary TB, but it is not possible to diagnose TB with chest x-rays alone (NIPH, 2013). The gold standard for diagnosing active TB is by culturing a sputum sample from the patient (CDC, 2013a). Another way of diagnosing tuberculosis is by direct microscopy of the sputum sample, although this is less sensitive than the culture (NIPH, 2013). Sensitivity is defined as the test's ability to give a positive result, given that the patient actually has the disease. Direct microscopy requires a large amount of bacteria per milliliter

sputum in order to be interpreted as positive, and if the direct microscopy is regarded as positive this indicates that the disease is more likely to be infectious (NIPH, 2013).

When it comes to latent TB, little is known and there is no gold standard for diagnosis. However, there are two tests that help in the immunological diagnosis of LTBI: The tuberculin skin test (TST, also called the Mantoux-test) and interferon-gamma release assays (IGRA).

The TST is conducted by injecting purified protein derivative (PPD, derived from tuberculin) under the skin of the forearm. If the patient has been exposed to the bacteria earlier a cell-mediated immunity to these antigens should occur, and a hypersensitivity reaction should cause an induration on the skin. The size of the induration should be measured 48-72 hours after the injection (CDC, 2013a). This requires the patient to have two contacts with health services: one for injecting PPD, and one for reading the test. Different cut-offs are used for concluding that the test is positive, and in Norway the cut-off is $\geq$ 6 mm (NIPH, 2013).

According to Pai et al. (2014) several issues should ideally be considered when interpreting a TST as positive. Aside from the size of the induration, the pretest probability of infection and the risk of disease if the person was infected should also be considered. Pai et al. mention two important causes of false positive TST results: Infection with non-tuberculous mycobacterium and prior bacillus Calmette-Guérin (BCG) vaccination. False positives as a result of BCG happen because the patient has been exposed to similar antigens earlier. The specificity of the test is lowered in those circumstances. Here specificity is the test's ability to produce a negative result given that the patient does not have LTBI. The degree to which BCG influences the specificity depends partly on when the BCG was given and partly on how many times it was given. For instance, if it was given at birth and not repeated the influence would be minimal (Pai et al., 2014).

There are two types of IGRA tests. The QuantiFERON-TB Gold In-Tube (QFT-GIT) and the T-Spot TB test (CDC, 2013a). These are blood tests that test the cell-mediated immune response (Pai et al., 2014). The proteins used in IGRA-tests are more specific for mycobacterium tuberculosis than the PPD used in TST, and are not shared with the strains in the BCG-vaccine. This makes the IGRA-test more specific in these cases (Nahid, Pai, & Hopewell, 2006). One benefit of the IGRA is that it is not as subjected to interpreter-bias as the TST and may not be as time-consuming since it only requires one contact with the patient.

The result of an IGRA-test can be available 24-48 hours after taking the test, but unfortunately the results may sometimes for differing reasons have low reproducibility (Pai et al., 2014).

Neither TSTs nor IGRAs can distinguish between LTBI and active TB, meaning that a positive result could mean both types (Delogu, Sali, & Fadda, 2013). Diagnosis of LTBI is based on obtaining a positive IGRA or TST and then eliminating the possibility of active disease with other tests such as chest x-ray and culture (NIPH, 2013). Since there is no gold standard, assessing the sensitivity and specificity of these tests needs to be done through other methods. One method to determine specificity is to use the tests on people who are assumed to have a very low risk of having LTBI. To determine sensitivity, active TB has sometimes been used as a surrogate for LTBI. One would then regard the test's ability to turn positive when a person has active TB as the sensitivity for LTBI.

Normally, positive predictive value (PPV) and negative predictive value (NPV) are defined as the probability that a person has the disease given a positive test, and the probability that the person does not have the disease given a negative test respectively (Hunink et al., 2001, p. 134). A recent meta-analysis by Diel, Loddenkemper and Nienhaus. (2012) that studied IGRA and TST used the terms in a different way. PPV in the study meant the probability that the patient would progress to active TB given a positive test, and NPV meant the probability of not progressing given a negative test. According to the study IGRAs have a higher PPV for progression to active TB and a higher NPV for progression than TST (Diel et al., 2012). Using PPV and NPV in this sense could potentially be a fruitful way of dealing with LTBI until a gold-standard is found.

2.3 Screening

In Norway screening for both active TB and LTBI is done. According to law, three groups of people undergo mandatory screening for active TB and LTBI (NIPH, 2013):

- People who come to Norway from a country with a high prevalence of tuberculosis and plan to stay for longer than three months, and asylum seekers and refugees.
- People working in health care and teachers who, during the last three years, have been in a country with a high prevalence of tuberculosis for at least three months.
- Other people who may have been infected or have been at risk of being infected.

NIPH defines high prevalence as a prevalence of 40 per 100 000 population. For LTBI, only people below the age of 35 are screened. This is because the risk of side effects is greater in older people and that younger people have a higher risk of reactivation.

Asylum-seekers and refugees undergo screening at Refstad, an asylum-center, where they take TST and chest x-ray and are referred to specialist health care (or primary health care in some instances) to take IGRA if TST is positive. Immigrants below the age of 15 do not take chest x-rays. Other immigrants (students, workers etc.) from high prevalence countries first take TST in primary health care and chest x-rays in specialist health care. They then take an IGRA-test if TST is positive. A new strategy is probably going to be introduced where TST is abandoned and screening is conducted using only IGRA. The IGRA-test will be then performed at Refstad instead of TST.

The Norwegian Institute of Public Health (NIPH) guidelines stipulate that if an individual is IGRA-positive and active TB has been excluded, the person should be put on preventive treatment if there is a sufficient risk that the bacilli may reactivate. Examples of risk-factors in the Norwegian guidelines are HIV-infection, immunosuppressant treatment, abnormal chest x-rays, being recently infected and being below 17 years of age, or an even higher risk below 5 years of age. The guidelines also say that the risk of side effects should be considered before starting treatment, unless there is a very high risk of reactivation (NIPH, 2013).

It is not known to what extent people are actually given treatment based on these risk factors, and some risk factors may not always be known. For instance, immigrants are offered an HIV-test, but not all of them take it.

2.4 Treatment

2.4.1 Active TB

Active TB should always be treated in order to get rid of the disease and stop further spreading (NIPH, 2013). The recommended medications for active TB are isoniazid, rifampicin, pyrazinamide and ethambutol so long as the TB is drug sensitive. The length of treatment recommended in Norway is 6 months, with one dose of medication taken every day. First there is an intensive phase were all these drugs are used, then after about 2 months it is recommended to reduce the medication to just isoniazid and rifampicin (NIPH, 2013). These

principles are recommended for both pulmonary TB and extra-pulmonary TB, but there are some exceptions such as tuberculous meningitis which requires longer treatment. The type of medications used MDR-TB or XDR-TB may vary and be different from these, but this is not considered further here because it is not part of the analysis.

Pulmonary TB requires hospitalization the first few weeks in order to prevent the infection from spreading. During this stay the patient is given medication and kept under watch. Before release from hospital or at the beginning of treatment for extra-pulmonary TB, a meeting is held where the patient, doctor, community nurse, tuberculosis coordinator and a nurse from the home services often participate. At this meeting the treatment is planned, and there is room for individual adjustments to the patient (NIPH, 2013).

When the patient is no longer in hospital, directly observed therapy (DOT) is normally used. This is when a nurse comes home to the patient every day to ensure that the patient takes the medication. In addition the patient is required to go to follow-up consultations with a doctor where new blood tests, chest x-rays and sputum samples are collected. This is to monitor the development of the disease and to watch for side effects. Before treatment is ended the patient is required to produce two negative cultures (NIPH, 2013).

During hospitalization, follow-up consultations and other contacts with the health system an interpreter is often required because the patients often do not understand Norwegian or English to a sufficient degree. This is paid for by the health care system (NIPH, 2013).

2.4.2 LTBI

LTBI is treated to avoid reactivation, and the treatment is often called preventive treatment or chemoprophylaxis. Guidelines made by the NIPH use a point system to determine whether someone should be put on preventive treatment or not. These points are given for risk factors associated with reactivation, some of which were mentioned in the previous section. Some risk factors are given more points than others, and if these exceed a certain level preventive treatment is recommended (NIPH, 2013).

The current recommendation for treating LTBI in Norway is to take rifampicin and isoniazid in combination for 3 months (3RH). Another commonly used regimen has been 6 or 9 months of isoniazid only (6H or 9H). The medication is taken once per day. Treatment meetings are also used for LTBI, and among the issues considered here is the need for DOT. For LTBI

whether the patient receives DOT or not depends on among other things if the patient understands why he/she is given treatment, and if the patient shows lacking motivation for taking the medication (NIPH, 2013). As with the treatment for active TB, treatment for LTBI requires the patient to have follow-up consultations with a doctor, although these are fewer than for active TB.

2.4.3 Side effects

Unfortunately, the medication for treating both active TB and LTBI can cause side effects. Isoniazid may cause clinical hepatitis (0.1%) and peripheral neuropathy (<0.2%) (CDC, 2013b). Rifampicin may among other things cause hepatotoxicity, nausea and skin reactions (CDC, 2013b). Side effects have important ramifications for treatment in several ways. Patients with LTBI do not feel ill, and may believe that the risk of developing active TB is low. This may cause them to drop out of or not accept treatment. Side effects are also one reason why people are not always put on treatment even though they are suspected of having LTBI. For both active and latent TB dropping out of the treatment may contribute to the development of resistant bacteria.

3 Health economic evaluation

3.1 Types of analyses and perspectives

Because resources are scarce, they need to be allocated in a way that ensures as much benefit as possible is produced from their use. This is also true for the health sector. Economic evaluation is a method used to help determine how to allocate resources (Briggs, Claxton, & Sculpher, 2006), and is a useful tool for improving decision-making by clearly identifying relevant alternatives (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005).

In health economic evaluation the most commonly used methods are cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). All of these examine both costs and consequences of health interventions, where costs are in terms of *opportunity costs*. Opportunity costs can be defined as the value of benefits of other alternatives that have been foregone by using resources on the alternative in question (Drummond et al., 2005). Common to CEA, CUA and CBA is that costs are measured in monetary terms. Each cost has to be identified, quantified and valuated. Identification means finding the costs that are relevant for the intervention of interest. The costs need to be quantified, which means putting a number on how much of the resource is used. Examples include the amount of visits to a general practitioner or how many tests are done. Valuation means putting a monetary value on the resource use (Drummond et al., 2005). Because people have a positive rate of time preference the costs also need to be adjusted for differential timing, which means that costs should be discounted if they occur in the future (Drummond et al., 2005).

The costs that are to be included depend on the perspective of the study. In a societal perspective, all resource use should be considered and transfer costs should not be counted. By transfer costs we mean costs that do not reflect resource consumption because they are only a transfer from one place to another (Drummond et al., 2005). The societal perspective measures the impact of an intervention on the whole of society. In a health-care perspective, only the resources used by the health care sector are counted. Transfer costs can be counted as long as they are transferred out of the health-care system. In the health-care perspective opportunity costs can be thought of in terms of other treatments/interventions foregone (Drummond, Weatherly, & Ferguson, 2008). It is also possible to only look at the costs

incurred for the patient, which would make it a patient-perspective. The societal perspective is generally regarded as the preferred type of perspective in health economics. This is because health economics is grounded in welfare economics, which regards society's welfare as the main concern (Byford & Raftery, 1998). Among the reasons why other perspectives are used are difficulty in obtaining data and difficulty measuring (Drummond et al., 2008).

What differs between CEA, CUA and CBA is the way we measure outcomes. In CEA we use natural outcomes related to the objective of the intervention, often intermediate, such the reduction in blood pressure and amount of infections cured (Drummond et al., 2005). By intermediate it is here meant that they do not directly reflect quantity of life (mortality) and quality of life (morbidity), but it is also possible to use more generic outcomes, such as survival.

Because many CEAs use outcomes that are specific for the disease they are of most use when comparing a limited set of options which use the same outcome. The downside of using this method is then that it does not allow for direct comparisons between programs looking at different diseases. Although the more generic measures can be used, they still do not capture both morbidity and mortality. A benefit of this approach is that it avoids the problems involved with valuing health states.

In CUA quality-adjusted life-years (QALYs) are used as an outcome. QALYs measure both changes in mortality and morbidity, and reflect the relative desirability of different health states (Drummond et al., 2005). Quality of life is measured by asking respondents to elicit their preferences for health states in different ways. According to Drummond et al. (2005), three common ways of measuring are the standard gamble, time trade-off and the visual analogue scale. The visual analogue scale presents the respondent with a line with endpoints, where one end implies the highest value and the other the lowest. The respondent is then asked to value a disease state on this line. The standard gamble presents the respondent with a health state, and he/she is asked to take a gamble between perfect health and death. The higher the probability of death the respondent accepts, the lower the utility of that health state is ranked. The time trade-off asks the respondent to make a choice between two alternatives. Either live in health state i for time t followed by death, or be in perfect health for time $x < t$ followed by death. Time x is then varied until the respondent is indifferent between the two alternatives, and the lower the value at which x is accepted, the worse the first health state is considered (Drummond et al., 2005).

An outcome-measure like the QALY has the benefit of trying to capture all aspects of the disease and can be useful for deciding amongst health programs that deal with different types of diseases. But there are also problems with QALYs. Among the questions raised against QALYs are questions about who should value the different health states, why many people seem unwilling to trade lifetime away and fairness issues (Nord, Daniels, & Kamlet, 2009).

In cost-benefit analysis the outcomes are valued in monetary terms. In principle one should implement programs where the benefits exceed the costs, although that may depend on certain things such as if one is operating within a fixed budget (Drummond et al., 2005). The benefit of this approach is that health interventions can in principle be compared to interventions in other sectors of the economy, and not just to other health interventions. One problem with this approach is that it is hard to assign a monetary value to benefits (Drummond et al., 2008).

There is a controversy on whether future outcomes should be discounted or not, and at what rate if they are to be discounted. The Norwegian Directorate of Health (2012b) recommend discounting both costs and outcomes at the same rate.

3.2 Decision analytic modelling

Decision analytic modelling is a tool used in economic evaluation. A decision analytic model can be defined as "a systematic quantitative approach to decision-making under uncertainty where at least two decision options and their respective consequences are compared and evaluated in terms of their expected costs and expected outcomes" (Gray, Clarke, Wolstenholme, & Wordsworth, 2011, p. 179). Expected costs or outcomes are simply costs or outcomes multiplied by the probability of them occurring. In economic evaluation decision analytic models use "mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated" (Briggs et al., 2006, p. 6). Although randomized controlled trials (RCTs) have sometimes been used to conduct economic evaluations, models have certain advantages. For instance they can be used for extrapolating data, synthesizing evidence, indicating the need and value of further research and comparing alternatives that may not have been compared in an RCT (Gray et al., 2011).

Commonly used models are the decision tree and the Markov-model. A decision tree is a model made up of branches, where each branch represents an event that could take place (Gray et al., 2011). Each branch consists of decision nodes or chance nodes. At each chance

node the branch is divided into further branches where each has a probability of occurring. As we move from left to right in the branches, a probability in a node to the right is conditional on all probabilities in the nodes to the left. Each branch has an associated cost and outcome associated with it. The expected costs and outcomes are then calculated for each branch by multiplying the costs and outcomes with the associated probability of moving through that branch.

Markov-models are models that make it easier to follow a cohort through time than decision trees, since time is explicitly defined in the model (Briggs et al., 2006). The model includes several mutually exclusive health states, such as healthy and ill. The cohort enters the model and remains in the health state for at least one cycle. One cycle is a defined period of time, for instance one year or one month. At the end of each cycle a person in the cohort can either move to another health state or remain in the same. This depends on the structure of the model and transition probabilities. States that it is not possible to move out from are called absorbing states (Hunink et al., 2001). If the data is presented in rates they need to be transformed to probabilities using Equation [1] below (Briggs et al., 2006).

$$p = 1 - \exp(-rt) \qquad [1]$$

Where *p* is the probability, *r* is the rate and *t* is the time unit.

If the probabilities or rates are not given for the same time period as the cycle length defined in the Markov model, further calculations are required. For instance, if a 5-year probability of an event to occur is given, the probability cannot simply be divided by 5 to obtain an annual probability. This is because that does not take compounding into consideration (Briggs et al., 2006). In order to calculate the annual probability, we need to go via rates by first converting the 5 year probability to a rate with Equation [2] (Briggs et al., 2006).

$$r = -[\ln(1 - P)]/t \qquad [2]$$

Second, we apply Equation [1] to convert the rate into an annual probability by using *t=1*.

Costs and outcomes are assigned to each health state in the Markov model and "rewarded" to each member that populates the health state for a cycle. All individuals in a given health state have identical characteristics (Gray et al., 2011), and the Markov-model does not record what

other health states a person in a given health state has been through. This is often referred to as the 'Markov assumption' (Drummond et al., 2005).

Models may be either probabilistic or deterministic. Deterministic models use point estimates of costs and probabilities and result in measures of costs and effects that are also point estimates. Probabilistic models use input parameters that are assigned a probability distribution in order to capture the uncertainty inherent in the parameters.

Which probability distribution is assigned will vary dependent on what type of parameter it is. Briggs et al. (2006) argue that there are only a few types of distributions that can be chosen for each type of parameter. For probabilities they suggest the beta distribution when the data is binomial. The beta distribution is characterized by the two parameters α and β, where α is the number of events of interest and β is the complement. A Dirichlet distribution is recommended when the data is multinomial, and is "the multivariate generalization of the beta distribution" (Briggs et al., 2006, p. 88). For costs they suggest the gamma distribution. The gamma distribution is characterized by α and β, where α is the squared sample mean divided by the variance and β is the variance divided by the sample mean (Briggs et al., 2006). A method called Monte Carlo-simulation is then used to randomly draw values from these distributions many times and make many different estimates (iterations) of the costs and effects of the intervention (Drummond et al., 2008).

When the structure of the model is completed and all costs, outcomes and probabilities have been entered into the model, we can produce estimates of expected costs and consequences. It is then a matter of how to present these results.

3.3 Presentation of results

3.3.1 Incremental cost-effectiveness ratio

Many methods for presenting the results of an economic evaluation exist, and the most frequently used is probably the incremental cost-effectiveness ratio (ICER). The ICER gives us the difference in costs between two interventions, divided by the difference in effects. The formula for calculating an ICER is given in Equation [3] taken from (Gray et al., 2011).

$$ICER = \frac{C_2 - C_1}{E_2 - E_1} \qquad [3]$$

Where the top part of the equation is the difference in costs between two interventions and the bottom part is the difference in effects. When calculating ICERs it is common to rank interventions from the least expensive to the most expensive, and calculate the ICER for each intervention compared to the one that is cheaper. The ICER will then say something about how much more has to be paid to achieve one more unit of effect.

After calculating ICERs, one should exclude the dominated (which means the strategy is more costly and less effective) or extendedly dominated strategies. Extended dominance is when the ICER of a given strategy is higher than that of the next, more effective alternative (Drummond et al., 2005). When making decisions based on the ICER the option with the highest ICER below the willingness-to-pay (WTP)-threshold should be chosen (Barton, Briggs, & Fenwick, 2008). This is shown in Equation [4].

$$\frac{\Delta C}{\Delta E} < \lambda \qquad [4]$$

The equation means that interventions are deemed cost-effective if the incremental costs (ΔC) divided by the incremental benefits (ΔE) are lower than the WTP per unit of effect (λ). The ICERs are often illustrated on a cost-effectiveness plane, as shown in Figure 2 on the next page. In probabilistic models there will be several estimates of the costs and effects of each intervention in this cost-effectiveness plane.

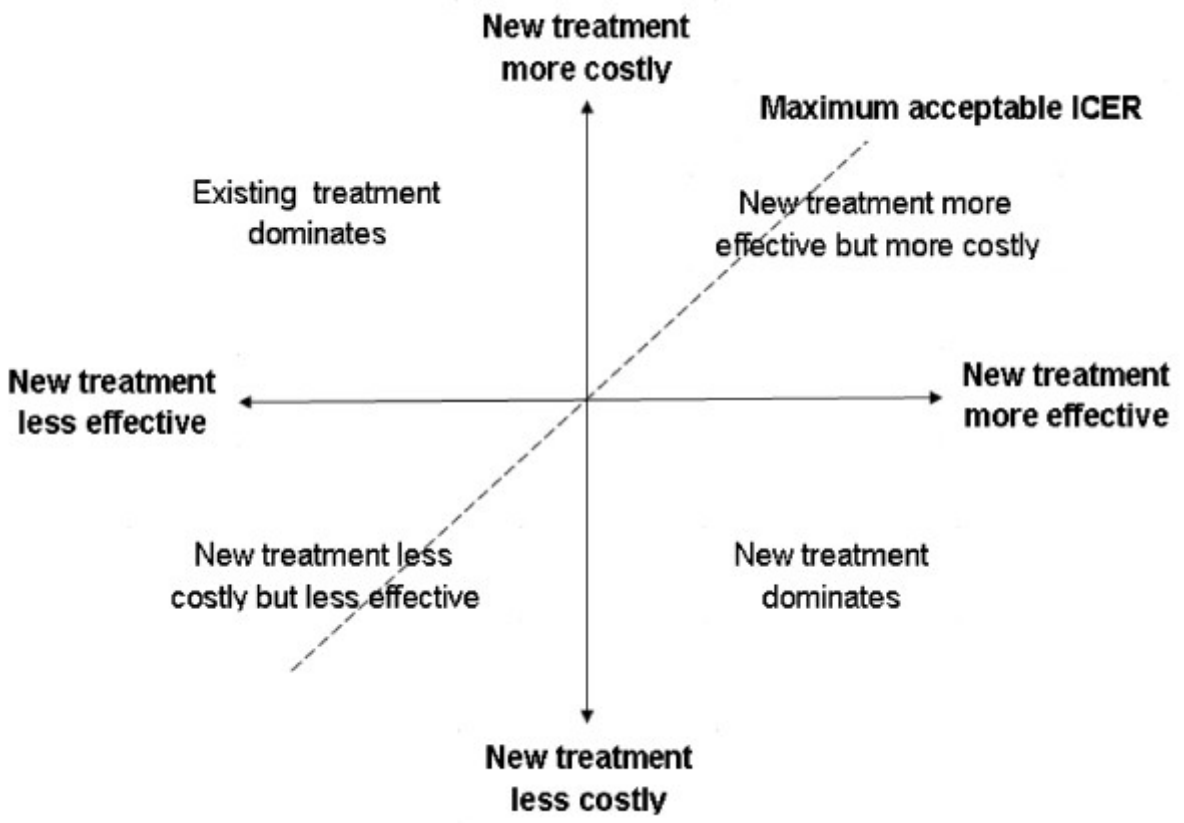

Figure 2 A cost-effectiveness plane (Hounton & Newlands, 2012)

The comparator is located in the origin. The other strategies can be more costly and more effective (north-east), less costly and more effective (south-east), less effective and more costly (north-west), or less effective and less costly (south-west) than the comparator. It is common for interventions to fall into the north-east quadrant, at least when the comparator is no intervention (Drummond et al., 2005). In a deterministic model we can plot point estimates of the interventions on the plane and draw a line between them (not illustrated in Figure 2). The slope of that line illustrates the ICER between the interventions (Drummond et al., 2005).

The WTP threshold per unit of effect is illustrated by the dotted line going through the origin denoted "Maximum acceptable ICER" in Figure 2, and all strategies falling below this line are considered cost-effective. As WTP increases, the line pivots around the origin in a counter-clockwise fashion. This means that if a strategy is located just above the WTP-threshold in the north-east quadrant, it could quickly become cost-effective if the WTP-threshold was increased.

ICERs may be difficult to interpret if they are negative. The reason is that an intervention with negative effects and positive costs can result in the same ICER as an intervention with

negative costs and positive effects (Drummond et al., 2005). Net monetary benefit (NMB) and net health benefit (NHB) have become frequently used methods of presenting results that do not have the same problems. They only involve a re-arrangement of Equation [4]. The formula for NMB is given in Equation [5] (Drummond et al., 2005).

$$NMB = \lambda * \Delta E - \Delta C \qquad [5]$$

Similarly, the equation can be rearranged to yield the NHB (Drummond et al., 2005):

$$NHB = \Delta E - \frac{\Delta C}{\lambda} \qquad [6]$$

All strategies with a NMB > 0 or NHB > 0 are considered cost-effective because the benefits produced by the strategy are below the willingness to pay for these benefits. When making decisions based on NMB or NHB, the strategy that results in the highest number should be chosen. In this study only NMB will be used and NMB is what will be meant by "net benefit" from here on.

3.3.2 Uncertainty

There are different types of uncertainty inherent in modelling. According to Briggs et al. (2006), these can be divided into variability, parameter uncertainty, decision uncertainty and heterogeneity.

Variability refers to the way that patients differ from each other. According to Briggs et al. (Briggs et al., 2006), it is hard to deal with the uncertainty resulting from variability and this will not be discussed further here. Parameter uncertainty refers to the precision of the estimate, for instance a probability or a mean cost entered into the model. Decision uncertainty refers to the fact that because parameters uncertain, there is a possibility that the wrong decision is made on the basis of them when entered into a model. Heterogeneity refers to part of variability which it is possible to explain by accounting for one or more of the patient's characteristics (Briggs et al., 2006).

Parameter uncertainty can be dealt with by applying probabilistic or deterministic sensitivity analysis (Briggs et al., 2006). Examples of deterministic sensitivity analysis are one-way analysis or scenario analysis. This involves changing the values of some of the parameters to see how their change influences the results. In one-way analysis we change the value of one

parameter at a time, while scenario analysis typically involves changing the value of multiple parameters to find results for a "best case" and a "worst case" scenario. It can also involve changing parameters to make scenarios that the analyst considers probable (Drummond et al., 2008). In probabilistic models parameter uncertainty can also be dealt with by Monte Carlo-simulation mentioned earlier. Using Monte Carlo-simulation to make several estimates in a cost-effectiveness plane can also be applied to decision uncertainty. However, it has been argued that cost-effectiveness acceptability curve (CEAC) must be constructed to graphically represent uncertainty associated with the estimated cost-effectiveness (Barton et al., 2008). The CEAC shows us the proportion of iterations from each strategy which are cost-effective for different values of the WTP-threshold. This can be interpreted as the probability that a strategy is cost-effective at each WTP-threshold (Barton et al., 2008).

It has been argued that decisions should be based on expected net benefit, and the strategy with the highest expected net benefit should be chosen no matter what the probability is (Barton et al., 2008). The strategy with the highest probability of being cost-effective in the CEAC may not always be the one with the highest expected net benefit. This is why the cost-effectiveness acceptability frontier (CEAF) is sometimes used (Barton et al., 2008). The CEAF shows the option with the highest expected net benefit for each value of the WTP-threshold, and the associated probability of it being cost-effective. Only the strategy with the highest expected net benefit is shown for each level of the WTP-threshold.

3.3.3 Expected value of perfect information

Decisions made on the basis of existing information will be uncertain, and even though the evidence suggest that a given strategy has the highest net benefit, this may not be the case with better evidence (Briggs et al., 2006). There are costs and foregone benefits associated with choosing the wrong strategy. Because perfect information could eliminate the possibility of making the wrong decision, the expected costs of uncertainty are interpreted as the expected value of perfect information (EVPI) (Briggs et al., 2006). EVPI is a way to determine the upper limit on the value of further research to eliminate uncertainty around a decision for different levels of the WTP-threshold. It is the maximum amount the decision maker should be willing to pay for perfect information (Barton et al., 2008).

In order to find EVPI we first we find the option with the highest expected net benefit across all iterations at a given WTP-threshold. This is the strategy that we would have picked at the

given WTP-threshold with current information. Second, we pick the strategy with the highest net benefit in each iteration and calculate the average for these (Barton et al., 2008). The reason this may differ from the one with the highest expected net benefit across all iterations, is that in some iterations the strategy picked may not be the one with the highest net benefit. We then subtract the net benefit found first from the net benefit found second. This difference is the EVPI for the given WTP-threshold. This process is repeated for all the WTP-thresholds we are interested in, and the results are plotted in a curve showing the EVPI for each WTP-threshold. The higher the probability of making the wrong decision and the higher the costs associated with it, the higher the EVPI will be (Briggs et al., 2006). Because of this EVPI will often peak at WTP-thresholds where two strategies have similar probabilities of being cost-effective.

It is also possible to calculate EVPI for different parameters or groups of parameters, which is called expected value of perfect parameter information (EVPPI). EVPPI is defined as the difference between expected net benefit with current information and expected net benefit with perfect information, and is useful for determining in which direction further research should be focused (Briggs et al., 2006).

Finding EVPPI is done in a similar way to EVPI. Following Briggs et al. (2006), to find the EVPPI for a given parameter at a given WTP-threshold, we first randomly draw a value from the parameter's probability distribution. We then keep this value constant while we do the regular Monte Carlo-simulation for all parameters. We then randomly draw a new value from its probability distribution and repeat the process. The process should be done many times, for instance by randomly drawing a value from a parameter's distribution 1000 times (inner loops) and doing simulations 1000 times for each value drawn (outer loops) (Briggs et al., 2006). Each time we are done with the outer loop we record the expected net benefit for each strategy. In addition we record the strategy with highest expected net benefit from each outer loop separately. We then take the expected benefit with perfect information and subtract the expected net benefit for the strategy with the highest expected benefit across all loops (Briggs et al., 2006). This is the EVPPI at the given WTP-threshold. These results can be presented in a bar chart with the x-axis showing the different groups of parameters or parameters and the y-axis showing the EVPPI (Briggs et al., 2006).

4 Research question

The question this study tried to answer was:

Which of the following screening strategies for latent tuberculosis in immigrants are cost-effective in a Norwegian setting: (1) No LTBI-screening, (2) screening only immigrants with risk factors, (3) screening with TST and IGRA, or (4) screening only with IGRA?

An area of particular interest is whether the probable forthcoming change of strategy from TST and IGRA to IGRA only is a cost-effective change, and what the budget impact will be. To establish cost-effectiveness the goal was to look at which strategies the highest expected net benefit at different levels of willingness-to-pay. It was also the hope that the study would contribute to the knowledge about what the screening for and treatment of TB costs in Norway. In addition the study tried to identify the main points of uncertainty and the potential value of further research using expected value of perfect information.

5 Methods

5.1 The model

5.1.1 Overview

In this chapter the model used for the CEA and then the details on input probabilities and costs will be described.

A combined decision tree and Markov model was developed in Excel. The different procedures the immigrants go through in this model were based on NIPH's guidelines on tuberculosis (NIPH, 2013), expert opinion at NIPH and personal communication with other people in the health system.

The model considered 4 screening strategies for LTBI:

1. No screening for LTBI (from here on referred to as "No screening" or "No LTBI-screening"). The immigrants go through chest x-rays and some go through HIV tests, but not IGRA or TST.
2. Screening only groups of people with risk factors for reactivation (HIV positive, abnormal chest x-rays) below the age of 35 from high prevalence countries for LTBI (from here on referred to as "IGRA risk"). The immigrants go through chest x-rays and some go through HIV tests, and in addition those with risk factors for reactivation take an IGRA test and are treated if IGRA is positive.
3. Screening all immigrants below the age of 35 from high prevalence countries with TST, and then IGRA if TST is positive (from here on referred to as "TST+IGRA"). This is the current strategy. The immigrants go through chest x-rays and some go through HIV tests, and in addition take a TST. If TST is positive they take an IGRA test and are treated if IGRA is positive.
4. Screening all immigrants below the age of 35 from high prevalence countries with IGRA only (from here on referred to as "IGRA"). This is the strategy that will most likely be adopted in the near future. The immigrants go through chest x-rays and some go through HIV tests, and in addition take an IGRA test. They are treated if IGRA is positive.

From here on, when immigrants are referred to in the model, they are always below the age of 35 and from countries with a high prevalence of TB, regardless of strategy. The model only looked at immigrant screening. People who are screened because they are going to work with children and/or in health care, and people who are screened as part of a contact investigation were excluded because of data limitations.

An illustration of the model is given in Figure 3. The complete decision trees can be found in Appendix I. The illustration shows the decision tree part on the left side, with boxes in blue and yellow. Immigrants move through the decision-tree from the left and end up in one of the Markov states on the right, illustrated by ellipses. The Markov model is denoted with colors orange, red and green. The decision tree part and Markov-model part will now be presented in turn.

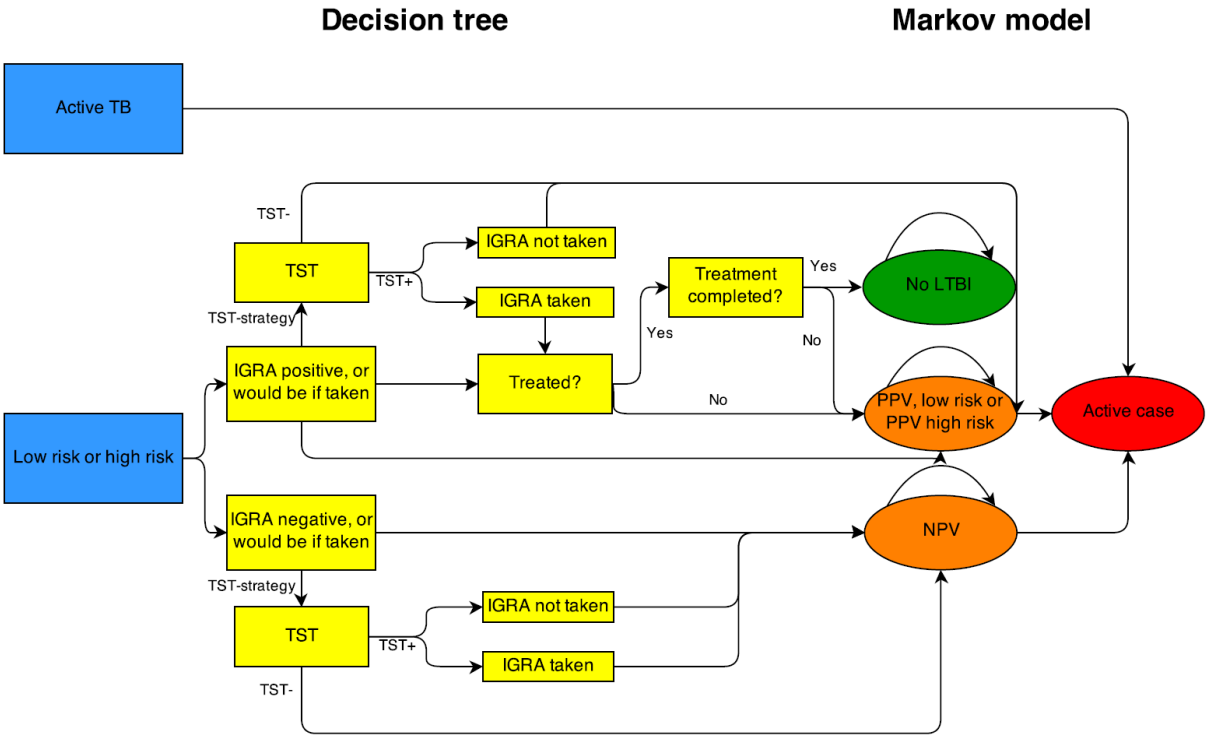

Figure 3 Illustration of the model

5.1.2 Decision tree

The blue rectangles are the starting points in the model, and consist of all immigrants who are eligible for screening. The top blue rectangle illustrates those that have active TB upon entering the country. These cases are assumed to be found no matter the strategy because

screening for active TB is done in all strategies. They are included because they also take LTBI-tests, and the types will differ from strategy to strategy.

The other blue box represents immigrants that are divided into groups depending on whether or not they have risk factors associated with higher probability of reactivation (high risk or low risk). They are illustrated in the same box because they go through identical decision trees. The difference between them is the Markov states they end up in. It is assumed that all have moved through the decision tree and into a Markov-state within a year from entering the model.

After the initial grouping, those who do not have active TB move to a branch depending on whether they get a positive IGRA-result or not, or which result they would have gotten had they taken the test. Because there is no gold-standard for diagnosing LTBI, no underlying prevalence of LTBI is assumed. Instead the model only takes into account what the result of the IGRA test was, or would have been if it had been taken.

After the initial IGRA/underlying IGRA the immigrants move through different branches depending on the strategy:

- In the no LTBI-screening strategy they move directly to a Markov-state depending on the underlying IGRA-result, i.e. PPV high risk, PPV low risk or NPV.
- In the IGRA risk-strategy, the group without risk factors moves directly to NPV or the low risk PPV state depending on the underlying IGRA result. The group with risk factors with a positive IGRA is considered for treatment, and if treated has a certain probability of completing treatment. If treatment is completed, it is assumed that there is no probability of reactivating and they move to the "No LTBI"-state. If treatment is not completed, it is assumed that they can still reactivate, and they move to the PPV-high risk state.
- In the TST+IGRA strategy both groups move to TST after the underlying IGRA. Here it is important to notice that IGRA precedes TST in the decision tree even though TST precedes IGRA in time in reality. Remember that for this strategy the first IGRA-result is an underlying result, the test is only taken if TST is positive. If TST is negative they move directly to a Markov starting state because after a negative TST IGRA is not taken. Whenever a TST is positive, IGRA can be taken or not. If it is not, the patient is considered missing and moves to the relevant Markov-state. According

to NIPH's guidelines, IGRA should always be taken if TST is positive. But sometimes the immigrants are not referred to the IGRA test or once they are referred they do not go. In reality, people could disappear if they have a negative TST as well, but this is of no consequence for the model as they would not get the IGRA-test anyway. Notice that it is possible to have both a positive and a negative TST after both an underlying a positive and an underlying negative IGRA.

- The IGRA-strategy is basically the same as the IGRA-risk strategy, except that the group without risk factors also takes an IGRA test and is treated if IGRA is positive.

5.1.3 Markov model

The Markov states in this simple Markov-model are "No LTBI", "PPV high risk", "PPV low risk", "NPV" and "Active case". Markov states with a risk of reactivation are labelled NPV or PPV because the probability of the groups inside these states reactivating is based on the negative predictive value and positive predictive value for reactivation. PPV can be either high risk or low risk, which denotes if people have risk factors associated with higher probability of reactivation or not. The states are represented in colors representing different risks of reactivation. Green means that there is no probability of reactivation, orange means that there is a probability of reactivation and red means that they are already active cases. The As illustrated in Figure 3, it is only possible to stay in the initial state or move to "active case", which is an absorbing state. In all strategies those that develop active TB or have active TB upon entry are treated. It is assumed that the treatment is started and completed in the same year as reactivation. All people who are in "No LTBI" stay there for the duration of the simulation.

The Markov model goes on for 10 cycles before it ends, representing 10 years. People who have not developed TB by then are assumed to not develop it at all. Ideally we would run the simulation for many more cycles. However, the evidence for reactivation was considered insufficient to extrapolate over such a long time. No half-cycle correction was performed on the Markov-model, and there is no death-state or possibility to die for other reasons because of the time horizon.

5.2 Literature review

The databases searched for data relevant for LTBI-screening, input probabilities, and economic evaluations: PubMed, Cochrane Library, Embase and Google Scholar.

Searches were focused on obtaining data on the progression to active TB from LTBI, evidence of IGRA/TST tests, cost-effectiveness of LTBI-screening and efficacy of treatment. Among main keywords used were: *latent tuberculosis, LTBI, screening, IGRA, QuantiFERON-TB, TST and Mantoux.* The keywords were used in combinations with other keywords such as: *cost-effectiveness, cost-utility, sensitivity, specificity, progression and reactivation.* Where relevant studies were found, the reference lists of the studies were searched for further relevant studies. There seemed to be no randomized controlled trials (RCTs) relevant for my cost-effectiveness analysis. Several Norwegian studies were found that were used as data in the model developed for this study. There were also studies looking at the specificity and sensitivity of TST and IGRAs, and one of these was a meta-analysis which was used in the model. Systematic reviews looking at economic evaluations for screening for LTBI and other economic evaluations for LTBI-screening were found. These are discussed in the discussion-section of this paper. They were also used to get an idea of how to develop a model for LTBI-screening. No Norwegian studies looking at the cost-effectiveness of LTBI-screening were found.

The studies found that were relevant are discussed in the discussion section of this paper.

5.3 Outcome and probabilities

5.3.1 Outcome

The outcome chosen for this analysis was avoided cases of active TB. The model produces active cases for each strategy, and the amount of avoided cases per strategy was calculated by comparing the amount of active cases that occur for the given strategy with the no-screening strategy (where no cases are avoided). The amount of active cases per strategy is defined as the amount of active TB cases upon immigration plus those that develop active TB during the 10 year simulation. Active cases were not discounted in the base analysis, although results with discounted active cases were also done as an alternative.

5.3.2 Probabilities

Decision tree

The data used in the decision tree are given in Table 1 on the next page. The distributions used in the probabilistic sensitivity analysis (PSA) are also given, together with the input required to establish the distribution. It was not possible to obtain data to establish a distribution for all parameters and this model is therefore only partially probabilistic.

All data used in the decision tree was based on Norwegian studies, data and/or expert opinion. The main source of data for the decision tree was a study by Winje et al. (2008). This study was used to establish data on the amount of IGRA-positive, active TB cases and the probability of getting a positive TST given different results on the IGRA test. The study was conducted at an asylum center in Norway. The probability of the immigrants having abnormal chest x-rays was obtained from a study by Harstad et al. (2009) also looking at asylum seekers. No data on the prevalence of active TB according to the risk group was found, so an identical prevalence of active TB in both groups was assumed.

Table 1 Input probabilities, alpha, beta, distribution and source(s) used in the decision tree

	Probability	Alpha	Beta	Distribution	Source(s)
Active TB	0.005	5	995	Dirichlet	(Winje et al., 2008)
Abnormal chest x-ray	0.07	323	4320	Dirichlet	(Harstad et al., 2009)
HIV-positive	0.02	130	6469	Dirichlet	Expert opinion
IGRA+	0.29	264	648	Beta	(Winje et al., 2008)
TST+, given IGRA+	0.88	232	32	Beta	(Winje et al., 2008)
TST+, given IGRA-	0.35	228	420	Beta	(Winje et al., 2008)
Probability of treatment	0.17	778	3798	Beta	MSIS+estimations
Probability of completing treatment	0.84	607	114	Beta	(Olsen et al., 2013)
Probability of missing after TST	0.2			None	Expert opinion
Probability directly observed therapy in LTBI-treatment	0.52	376	345	Beta	(Olsen et al., 2013)
Probability of taking voluntary HIV-test	0.8			None	Expert opinion

The probability of being HIV-positive and the probability of taking a HIV test were based on expert opinion at the NIPH. As can be seen from the table the probability of taking an HIV-test is 80%, which means that we will in reality not know the HIV-status of 20% of the immigrants. One simplification made here is then that the group without risk factors consists of people who have an unknown HIV-status. These 80% take the HIV-test regardless of strategy.

HIV-positive and people with abnormal chest x-rays together constitute the group with risk factors. The group without risk factors is the complement of active TB, abnormal chest x-rays and HIV-positive.

The parameter for the amount missing following a TST was estimated by expert opinion. It is only possible to go missing after both injection and reading, which is a simplification.

The parameter for the probability of being treated following a positive IGRA was based on calculations. The amount of LTBI-treatments started is reported to the Norwegian Surveillance System for Communicable Diseases (MSIS), while the amount of positive IGRAs is not. That is why data on the proportion of IGRA-positive results from tests analyzed at Oslo University Hospital (OUS) were obtained and assumed to be equal for the whole

country. The total amount of LTBI-treatments given in Norway was then divided by the number of positive tests to obtain the probability of being put on treatment given a positive IGRA. From 2011 to 2013 there were 778 people put on preventive treatment each year on average. Country-wide there were 15780 IGRA-tests analyzed in 2013 (personal communication). According to OUS 29% of their tests are positive. If we assume that all preventive treatments are a result of a positive IGRA and that the proportion IGRA positive tests are the same for the whole country we find the probability to be about 0.17. A simplification made is that this probability is equal for both risk groups. The impact of this assumption will be investigated in the sensitivity analysis.

There is also a probability that people will not complete treatment once treatment has been initiated. The probability of completing treatment and being put on DOT for LTBI is based on a cross-sectional study by Olsen et al. (2013). There may be several reasons why people do not complete treatment, for instance there may be side-effects that cause the patient to stop. It was assumed that people in the high risk group and low risk group have an equal probability of being treated and completing treatment given positive IGRAs. The assumption that people in the high risk group have an equal probability of being treated will be explored in the sensitivity analysis.

Markov model

In this study it was decided to use PPV and NPV for progressing to active TB based on the results of the IGRA as transition probabilities. The probabilities for progression were found in the meta-analysis by Diel et al. (2012) previously mentioned. The authors in this analysis made PPV estimates for people with risk factors and for groups without for both IGRA and TST. In the model only the PPV and NPV for IGRA were used to ensure the same amount of active cases would be produced in all strategies if none were treated. In addition IGRA has the highest values on PPV and NPV which makes it best at prediction activation.

Risk factors in the meta-analysis were defined according to the American Thoracic Society/Centers for Disease Control criteria, which means HIV-infection, recent infection, chest x-ray findings indicating previous infection and weight (American Thoracic Society, 2000). The studies the meta-analysis was based on were conducted in both low-prevalence countries and high-prevalence countries. The meta-analysis used data from a total of 15 studies with 1 436 participants to establish PPV for the group with risk factors. To establish

the PPV in the group without risk factors data from 19 studies with a total of 5 194 participants were used. The studies looking at people with risk factors also contained people without risk factors, and these same studies were used in the estimate of both PPVs. The meta-analysis did not separate between the two risk groups when it came to NPV, so NPV in this model is the same for both. There were 24 studies used for NPV estimation, with a total of 12 154 study participants.

The follow-up time in the studies ranged from 1 year to 46 months, and the PPV was the probability of developing active disease within this time. These probabilities needed to be transformed to annual probabilities for the Markov-model using Equation [1] and [2]. After going through the studies the meta-analysis was based on, the median follow-up time for each study was found and used as a basis for calculating rates. *t* in Equation [2] was the weighted mean (weighted by amount of participants in the studies) of the median follow-up times. *t* was 2.19 for the PPV in the high risk studies, 2.42 for the PPV in the low risk studies and 2.19 in the NPV studies. The rate found was then transformed to an annual transition probability with Equation [1], where *t* was set to 1 year. The results of these calculations are the numbers under the headline "Annual probability" in Table 2.

Table 2 Input probabilities and source(s) used in the Markov model

Progression probabilities	Probability	Follow-up (years)	Alpha	Beta	Distribution	Annual probability	Source(s)
NPV	0.003	2.31	12 113	41	Beta	0.001	(Diel et al., 2012)
PPV, high risk	0.068	2.19	98	1 338	Beta	0.032	(Diel et al., 2012)
PPV, low risk	0.027	2.42	141	5 053	Beta	0.011	(Diel et al., 2012)
Decline, reactivation probability	0.57	10			None	0.081	(Wiker, Mustafa, Bjune, & Harboe, 2010)

In the model the annual probabilities of progressing to active TB declines with about 8% each year. The decline is based on a study by Wiker et al (2010) who calculated the 10 year decrease in progression rate as being 57% on average. In my model this was used to mean that the annual transition probabilities were reduced by 57% over 10 years, and this was transformed to an annual reduction with Equation [1] and [2]. In this model the decline only starts after the two first years. The reason for this is that this is approximately when the

follow-up from the meta-analysis stops and the extrapolation begins. Reduction in risk also seems to occur after the first few years after immigration (Pareek et al., 2011)

5.4 Costs

This section will give an overview of the costs of screening and treatment used in this study, and they can be found in Table 3 and 4 respectively. A more detailed table on the estimation of costs used in this model can be found in Table I in Appendix II. All costs were point estimates that were assigned a gamma-distribution with a standard deviation of 10% in the probabilistic model. They were estimated from a health budget perspective.

The costs that needed to be identified were the costs of screening for and treatment of both LTBI and active TB. As mentioned these were identified with the help of NIPH's guidelines and expert opinion. Unfortunately no patient-level data on costs was found. This means that the quantification of costs incurred were based on NIPH's guidelines and expert opinion, and not on the actual use of resources.

The valuation of costs came from different sources, including reimbursement rates (Diagnosis related groups (DRGs) and fee-for-service (FFS)), wage rates and market prices. Most costs came from reimbursement rates. FFS rates were, following guidelines by the Directorate of Health (2012b), multiplied by two to approximate true costs. Also following these guidelines, all future costs were discounted at 4%. Value-added tax (VAT) was excluded from the analysis, and all costs were adjusted to year 2013.

5.4.1 Screening

Table 3 Costs associated with screening

	NOK	Source(s)
IGRA	386	(Forskrift om utgifter til poliklinisk helsehjelp, 2013; Statistics Norway, 2013), expert opinion
TST	168	(Statistics Norway, 2013), expert opinion
HIV-test	146	(Forskrift om utgifter til poliklinisk helsehjelp, 2013; Norwegian Medical Association, 2013), expert opinion
Chest x-ray	504	(Forskrift om dekning av laboratorieutgifter, 2013)

The relevant screening tests were the TST, IGRA, HIV-tests and chest x-rays. As mentioned in the section describing screening, these tests may be taken in different locations. In the model it was assumed that the costs are the same no matter where they are taken.

The costs for TST were based on labor and material costs. The labor costs were based on time estimates made by Oslo Municipality and NIPH, and the material cost was the cost of tuberculin which was provided by the NIPH (NIPH, 2014). Hourly wages were based on the average hourly wage of nurses found at Statistics Norway (Statistics Norway, 2013).

The costs of IGRA can be divided in two: The costs of taking the test (drawing blood), and the costs of analyzing the test. The cost of taking the test was the cost of labor time. The costs of analyzing the tests at the laboratory were based on the reimbursement rates provided by OUS. These rates were assumed to cover the costs of the IGRA-kit required to take the test.

The costs of a chest x-rays were based on reimbursement rates for laboratories plus the user charge to patients. The user charge for patients was included because this charge is in reality covered by the health system. Chest x-rays are taken by everyone in the screening process, but in reality chest x-rays are also taken during follow-up consultations for active TB. These were assumed to be covered by the DRG for follow-up consultations.

The costs of taking a HIV-test was based on the fee schedule for general practitioners, and reimbursement fees for laboratories for analyzing the tests.

5.4.2 Treatment

The relevant treatment costs are listed in Table 4 on the next page, with separate estimates for the three types of treatment: Pulmonary TB, extra-pulmonary TB and latent TB. The treatment costs can be divided into medication costs, laboratory costs and hospital costs. The expected costs of active TB at the bottom of the table were based on the fact that about 70% of active cases in Norway are pulmonary and the 30% extra-pulmonary (Arnesen et al., 2013).

Table 4 Costs associated with treatment

	Pulmonary TB (NOK)	Extra-pulmonary TB (NOK)	Latent TB (NOK)	Source(s)
Medication costs				
Intensive phase	1 467	1 913	0	(NIPH, 2013; Norwegian Medicines Agency, 2014b)
Follow-up phase	1 511	1 511	0	(NIPH, 2013; Norwegian Medicines Agency, 2014b)
LTBI-drug regimen			1 133 (-50% for partial treatment)	(NIPH, 2013; Norwegian Medicines Agency, 2014b)
Hospital costs				
Hospitalization	106 349	0	0	(NIPH, 2013; The Norwegian Directorate of Health, 2012a), expert opinion
DOT	24 485	26 550	6 903 (-50% for partial treatment)	Market price, (NIPH, 2013; Olsen et al., 2013) About 52% get DOT for LTBI (Table 1)
Follow-up consultations	6 784	6 784	3 392	(NIPH, 2013; The Norwegian Directorate of Health, 2012a)
Interpreter	6 752	6 752	1 688	Market price, hospital accounts, assumed for LTBI
Treatment meeting	1 521	1 521	1 521	(Statistics Norway, 2013), expert opinion
Sputum sample	106	106	106	(NIPH, 2013; Statistics Norway, 2013) expert opinion,
Laboratory costs				
Blood test	192	192	192	(NIPH, 2013; Norwegian Medical Association, 2013)
Laboratory analyses	2930	2930	198	(Forskrift om utgifter til poliklinisk helsehjelp, 2013; NIPH, 2013),expert opinion
	152 097 (*70%)	48 259 (*30%)	15 133	
Costs, active TB	**120 946**	**Costs, LTBI**	**15 133**	

Medication costs

The medication costs were identified and quantified using NIPH's guidelines, and price of the medication was found in the Norwegian Medicines Agency's database (Norwegian Medicines Agency, 2014b).

The treatment for active TB in this model consisted of isoniazid, rifampicin, pyrazinamide and ethambutol for two months (the intensive phase), and thereafter isoniazid and rifampicin for four months (the follow-up phase) (NIPH, 2013). The brands of drugs used were Rimstar for the intensive phase and Rimactazid for the follow-up phase. According to OUS a pulmonary TB patient normally spends about 14 days in hospital, and for pulmonary TB the amount of days spent in hospital was subtracted from these 6 months since DRG covers medication. LTBI-treatment was 3 months of rifampicin and isoniazid taken every day, and the brand used was Rimactazid. The amount of each type of drug taken in this model was calculated based on an assumption of a 70 kg person.

All treatments for active TB used DOT in this model. For pulmonary TB the number of days spent in hospital was subtracted from the full days of DOT. As seen from Table 1 in the probabilities section, only about 52% of patients treated for LTBI receive DOT, so the full costs of DOT were multiplied by 0.52 here. The costs for DOT were based on the prices that Oslo Municipality pays to UNICARE, a private company.

Strictly speaking the drugs used for LTBI and for active TB following hospitalization is not paid for by the health system, but by the National Insurance Scheme. These costs were still included in the analysis because they were found to fall under health care costs.

Hospital costs

The hospital costs in this model were the costs of hospitalization, follow-up consultations, interpreter, treatment plan meeting and blood tests.

In the model the cost of the hospitalization was based on the reimbursement received by the hospitals through activity based funding. The relevant DRG was identified, and the costs calculated (The Norwegian Directorate of Health, 2012a). As mentioned the DRG is supposed to cover all procedures done during hospitalization, including medication and overhead costs.

The treatment meeting is a meeting lasting about an hour and who attends the meeting varies some. In this model the costs of a doctor, a tuberculosis-coordinator, a nurse and a representative from the home services were included.

For extra-pulmonary TB, LTBI, and for pulmonary TB after hospitalization, the patient has to visit an outpatient clinic during treatment to take blood samples, sputum smears for direct microscopy and culture, and chest x-rays. According to NIPH guidelines this happens about 4 times for active TB and 2 times for LTBI. The cost of a follow-up consultation was based on DRG, and these rates were assumed to cover the chest x-rays, sputum samples and blood tests taken in connection to these consultations. Therefore, the sputum samples and blood tests listed in Table 4 are the sputum samples and blood tests taken in addition to these follow-up consultations. The cost of obtaining a sputum sample outside the follow-up consultations was based on labor time using time estimates provided by OUS.

Interpreter costs were based on the accounts from OUS, with an average use of 8 hours per patient and an average wage of NOK 844. These costs only include the average interpreter cost per patient with pulmonary tuberculosis, but it was assumed that the same amount of hours is used for extra-pulmonary TB. No data on the use of interpreter for LTBI was found, and was simply assumed to be considerably less at 2 hours.

Laboratory costs

The relevant laboratory costs were those of analyzing the blood tests and the different procedures conducted on the sputum samples. This includes direct microscopy, direct PCR (polymerase chain reaction), resistance determination, culture, and identification. All these costs were based on laboratory reimbursement rates, and the relevant rates were provided by OUS. The analysis of blood tests consists of CRP (C-Reactive protein) and 9 other tests. As mentioned most blood tests were assumed to be covered by DRG, except for the first test for every treatment. These are the ones listed in Table 4.

5.5 Important simplifications and summary of the model

Creating a model involves making simplifications of reality. Some of these are summarized below, and are sorted depending on whether they will be discussed/explored in the sensitivity analysis, or if they will not. Table 5 on the next page provides a summary of the important features of the model.

Simplifications that are discussed in the discussion and/or part of the sensitivity analysis:

- No background mortality or deaths from TB.
- Completed preventive treatment means no risk of reactivation.
- Incomplete treatment means no effect of treatment.
- All individuals with active TB start and complete treatment with full efficacy.
- No active cases infect others.
- The probability for being put on treatment is the same for both risk groups.
- The probability of getting a positive IGRA result is the same for both risk groups.
- The cost of treating MDR-TB is not included.
- No side-effects from treatment
- Results of HIV tests are known for the 80% before choosing to screen, even though in reality many results may not be available until a time after screening
- All immigrants take the LTBI-test relevant for the strategy

Other simplifications that will not be discussed further:

- Screened individuals can only go missing after both parts of the TST, i.e. injection and reading.
- All those who enter the model go through chest x-ray, although in reality children below the age of 15 do not.
- Individuals with a TST resulting in an induration of over 15mm that do not get a positive IGRA are not considered for treatment in this model.

Table 5 Summary of the cots-effectiveness analysis

Main issues	
Type of model	Combined decision tree and Markov-model
Type of economic evaluation	Cost-effectiveness analysis
Comparators	4 screening strategies: 1. No screening for LTBI (baseline) 2. Screening risk groups with IGRA 3. Screening with TST+IGRA (current strategy) 4. Screening with IGRA
Perspective	Health budget perspective
Patient group	Immigrants below the age of 35 from countries with high prevalence of TB
Time horizon	10 years
Outcome	Avoided cases of active TB
Unit costs	Market prices, fee schedules, DRG, estimations, wage rates.
VAT	Excluded
Year of costs	2013
Discount rate (costs) **Discount rate (effects)**	4% Not discounted in the base analysis
Sensitivity analysis	One-way, scenario, probabilistic

6 Results

6.1 Costs and health consequences

Table 6 shows the deterministic results per screened immigrant. Results when the extendedly dominated strategy is included are shown in square brackets. A cost-effectiveness plane resulting from 5000 iterations is shown in Figure 4 on the next page. The ICERs for the probabilistic results were almost identical to the ones in Table 6, and are not shown.

Table 6 Deterministic results per screened individual. Results with extendedly dominated (ED) strategy included in square brackets

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	4 756	0	0.0400	Baseline	Baseline	Baseline
IGRA risk	4 775	0.0008	0.0392	19	0.0008	23 760
TST+IGRA	5 303	0.0027	0.0373	ED [528]	ED [0.0019]	ED [272 728]
IGRA	5 459	0.0039	0.0361	684 [155]	0.0031 [0.0012]	221 008 [134 343]

In the deterministic results the expected cost per screened immigrant according to strategy ranged from NOK 4 756 to NOK 5 459, with the IGRA-strategy being the most costly. The effectiveness of the strategies increased with costs, and the amount of avoided cases was 0.0008 with the IGRA risk strategy going up to 0.0039 with the IGRA strategy. Moving from the TST+IGRA-strategy to the IGRA-strategy would cost NOK 134 343 per additional avoided case of active TB. According to these results, TST+IGRA was not cost-effective as it was extendedly dominated. When removed, the resulting ICER for the IGRA-strategy was NOK 221 008.

A rough estimate made by the NIPH on the amount of immigrants actually screened each year is 16 000, and deterministic results for a cohort of 16 000 is shown in Table 7 on the next page. According to these results, a cohort of 16 000 screened immigrants would cost about NOK 85 million over 10 years with today's strategy. Moving to the IGRA strategy from TST+IGRA would cost an additional NOK 2.5 million and avoid 18.5 more cases. Moving from TST+IGRA to IGRA risk would reduce costs by about NOK 8.5 million, but would also reduce the amount of avoided cases by 31. The no LTBI-screening strategy would cost about NOK 300 000 less than the IGRA-risk strategy.

Table 7 Table showing deterministic results for a cohort of 16 000. Results with extendedly dominated (ED) strategy included in square brackets

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	76 091 451	0	639.9	Baseline	Baseline	Baseline
IGRA risk	76 395 534	12.8	627.1	304 082	12.8	23 760
TST+IGRA	84 851 190	43.8	596.1	ED [8 455 657]	ED [31.0]	ED [272 728]
IGRA	87 336 890	62.3	577.6	10 941 357 [2 485 700]	62.3 [18.5]	221 008 [134 343]

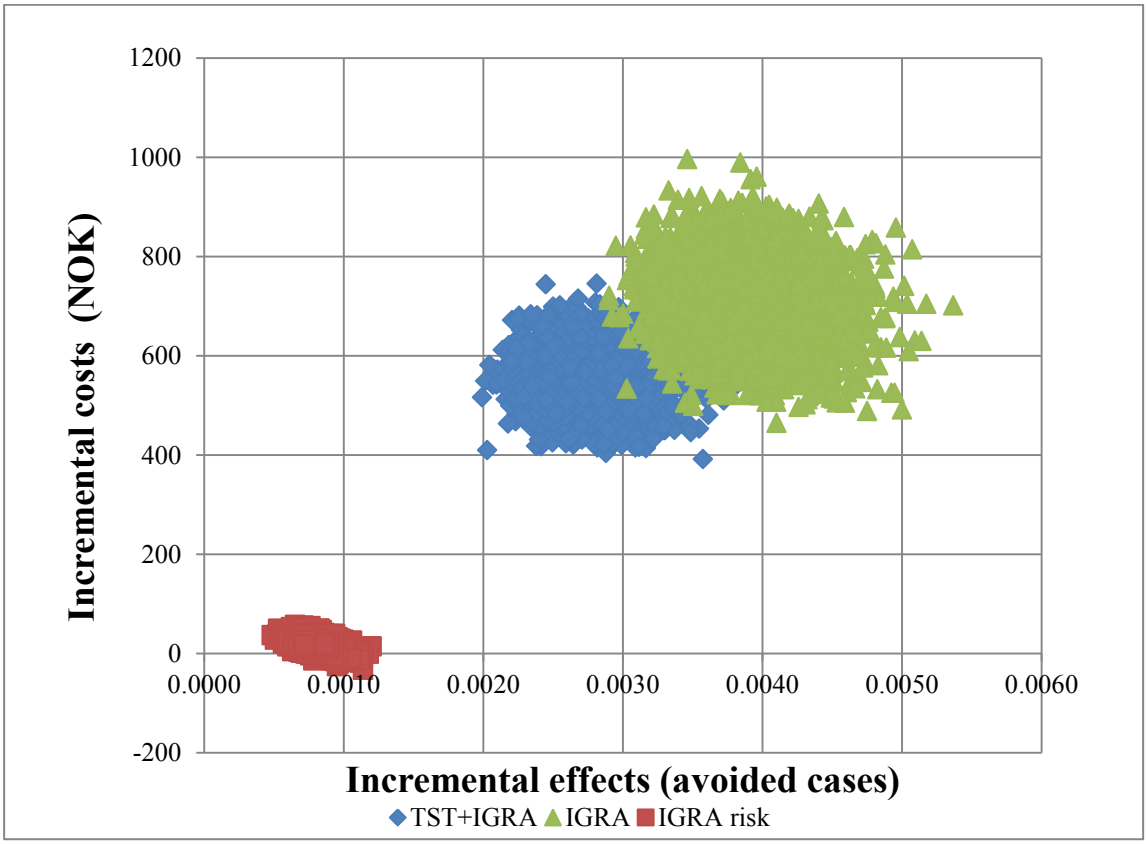

Figure 4 Cost-effectiveness plane showing the results of 5000 iterations. Results per screened immigrant.

The cost-effectiveness plane in Figure 4 shows the north-east quadrant and a part of the south-east quadrant. The no screening strategy is located in the origin, which means that the costs and effects of the other strategies are displayed incremental relative to the no screening strategy. Almost all iterations were in the north-east quadrant, meaning that the strategies that involved screening for LTBI cost more and were (naturally) more effective than no-screening. It looks as if the IGRA risk-strategy in some iterations was cost-saving compared to no screening. The TST+IGRA and IGRA strategies in many iterations overlap, which means they had similar costs and effects in those cases. Still, it seems that most of the IGRA-strategy iterations were located to the east and north from the TST+IGRA strategy meaning it was

more expensive and more effective. Judging from Figure 4 it does not seem like the results found in Table 6 are sensitive to changes in the parameters resulting from the Monte Carlo-simulation.

A cost-effectiveness plane displaying the deterministic results with a cost-effectiveness frontier can be found in Appendix III. Since the main analysis did not include results when avoided cases were discounted, Table III in Appendix IV shows the results when both costs and avoided cases are discounted at the same rate (4%).

6.2 Sensitivity analysis

6.2.1 Deterministic sensitivity analysis

Several one-way analyses and scenario analyses were performed to supplement the probabilistic results in Figure 4, and to get a clearer view of how the parameters influence the results. In all cases the TST+IGRA strategy remained extendedly dominated, but some are still worth commenting on. Table 8 on the next page shows some one-way analyses, of which not all will be commented on. One-way analyses for other parameters and more values of the parameters can be found in appendices VI and VII.

It may be argued that both the costs of a TST and the treatment of active TB are higher than in the base estimate. TST costs may be higher because sometimes effort has to be put into getting people to meet up for the test. Costs of active TB may be higher because MDR-TB is not included in this analysis, and because the DRG costs for hospitalization may not fully cover the costs. Table 8 shows that if the cost of a TST increased to NOK 325 (from NOK 168 in this study), the ICER for the IGRA-strategy became negative when TST+IGRA was included in the results. In this case that meant IGRA is cost-saving compared to TST+IGRA, because the costs were lower and avoided cases higher (not seen in Table 8). The table also shows that if the cost of treating active TB is increased, the ICERs for the strategies that involve screening for LTBI are lowered. At NOK 175 000 per treated active case, IGRA risk became cost saving compared to no LTBI-screening. When the costs of the IGRA-test were higher, all strategies that involved screening became more unattractive (higher ICERs).

Table 8 One-way sensitivity analysis for some chosen parameters

Results with extendedly dominated strategies included shown in square brackets. Empty brackets mean it is equal.

	Base estimate	Values explored	IGRA risk (ICER)	TST+IGRA (ICER)	IGRA (ICER)
Probability of being missing after TST	0.2	0	23 760 []	ED [237 556]	221 008 [129 077]
		0.4	23 760 []	ED [346 314]	221 008 [135 693]
Probability IGRA-positive, high risk group only	0.29	0.39	12 034 []	ED [286 608]	221 008 [122 772]
		0.59	589 []	ED [318 250]	221 008 [103 798]
Probability treated, high risk group	0.17	0.5	-6262 []	ED [364 662]	221 008 [89 855]
		0.9	-13137 []	ED [599 937]	221 008 [61 201]
Annual reactivation probability, low risk group	0.011	0.0025	23 760 []	ED [2 706 764]	1 312 588 [507 961]
		0.0075	23 760 []	ED [490 777]	378 344 [217 384]
Annual reactivation probability, high risk group	0.032	0.0045	ED [705 313]	ED [237 612]	239 693 [183 857]
		0.0200	89 989 []	ED [257 521]	221 008 [152 369]
Cost, IGRA	386	300	13 624 []	ED [258 871]	195 834 [90 205]
		500	37 194 []	ED [291 097]	254 378 [192 851]
Cost, TST	168	100	23 760 []	ED [237 724]	221 008 [192 998]
		325	23 760 []	ED [353 838]	221 008 [-1 568]
Cost, active TB	120 946	75 000	62 265 []	ED [311 016]	259 319 [172 694]
		175 000	-21 541 []	ED [227 683]	175 935 [89 223]
Cost, latent TB	15 133	10 000	-4 435 []	ED [193 164]	147 053 [69 788]
		20 000	50 489 []	ED [348 157]	291 118 [195 542]

It may also be argued that the 17% estimate of the amount treated following a positive IGRA was too low for the group with risk factors, because these would more often be put on treatment because of higher risk of reactivation. It was thought that the probability distribution used for this parameter would not fully take this into account. As seen in Table 8 and in Appendix VI, making the probability higher lowered the ICER of the IGRA risk-strategy, while the ICER for IGRA strategy stayed the same. When TST+IGRA was included the ICER for the IGRA strategy was lowered. IGRA-risk dominated no LTBI-screening at a 50% probability of treatment, with lower costs and higher effects (not seen in Table 8).

The probability of having a positive IGRA may in reality be higher for people with risk factors because they have a higher risk of being infected. When the probability was increased, the ICER fell for IGRA risk, while it stayed the same for IGRA. When TST+IGRA was included, IGRA became more attractive (lower ICER) the higher the probability.

The estimate on how many people went missing following TST was a very uncertain parameter, based only on expert opinion. In addition it did not have a probability distribution in the probabilistic model. When including TST+IGRA, the one-way sensitivity analysis shows that increasing the probability of being missing after TST increased the ICER of both TST+IGRA and IGRA. The ICER of IGRA increased because the costs of TST+IGRA were reduced the higher the probability became (not shown in Table 8). TST+IGRA was extendedly dominated at all values of the parameter.

It is common in the tuberculosis literature to use a lower reactivation probability than is used in this study, often 5% to 10% probability during a person's lifetime (often defined as 20 years). In the one-way sensitivity analyses and scenario analyses the reactivation probability was varied. As with the other one-way sensitivity analyses, TST+IGRA remained extendedly dominated. As can be seen in Table 8, when the annual reactivation probability for the group with risk factors became sufficiently low, IGRA risk was extendedly dominated. Lowering the probability for the low risk group increased the ICERs of TST+IGRA and IGRA.

The scenario analysis in Table 9 shows the results after the annual reactivation probability was set to 0.0025 for the low risk group, 0.0045 for the high risk group and 0 for the ones with negative IGRA. This results in about 2.5% reactivating in the low risk group and 4.5% in the high risk group over 10 years, which is closer to the probabilities commonly used in the literature (Oxlade, Pinto, Trajman, & Menzies, 2013). Since an objection to the model may be that it is not possible for active cases to infect others, reactivated cases also infected 0.2 other people with active TB. This is a number borrowed from Pareek et al. (2011).

Table 9 Result of a scenario analysis with annual reactivation probabilities lowered and 0.2 additional active cases per reactivated case. Results with extendedly dominated (ED) included in square brackets.

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	2 123	0	0.0141	Baseline	Baseline	Baseline
IGRA risk	2 204	0.0002	0.0139	81	0.0002	413 079
TST+IGRA	2 857	0.0009	0.0132	ED [653]	ED [0.0007]	ED [900 794]
IGRA	3 091	0.0013	0.0128	887 [234]	0.0011 [0.0004]	796 387 [601 789]

The results show that the ICERs increase substantially, with the ICER for IGRA being about NOK 800 000 and the ICER of IGRA risk being about NOK 413 000. TST+IGRA remained extendedly dominated. One scenario with only 0.2 infected for each reactivated case, and one scenario with only reduced reactivation probabilities can be found in Appendix V.

6.2.2 Probabilistic sensitivity analysis

For the probabilistic model a cost-effectiveness acceptability curve and a cost-effectiveness acceptability frontier were constructed. Expected value of perfect information was calculated both in total and for groups of parameters.

Figure 5 on the next page shows the CEAC, and there are two points at which the strategy having the highest probability of being cost-effective changes. Up to a WTP-threshold of NOK 24 000 the no LTBI-screening strategy has the highest probability. From there until NOK 222 000 it is the IGRA-risk strategy. From there and upwards it is the IGRA-strategy. These thresholds more or less reflect the ICERs when the extendedly dominated strategy was excluded from the analysis. In the deterministic sensitivity analysis some parameters were changed in such a way that the ICERs for some of the strategies increased. That change would cause the WTP-threshold needed for the given strategy to be cost-effective to increase. In the CEAC, TST+IGRA is not cost-effective at any threshold of WTP.

In Figure 6 the CEAF is plotted together with the expected value of perfect information per screened individual. The CEAF shows us that the strategies with the highest expected net benefit at different WTP-thresholds are more or less consistent with which one has the highest probability of being cost effective shown in Figure 5. EVPI also peaks at the WTP-thresholds where the strategy having the highest probability of being cost-effective changes. The chance of picking the wrong strategy at these WTP-thresholds is relatively high, around 50%, which is why the EVPI is so high. The second peak has the highest EVPI, and this is where the optimal strategy changes from IGRA risk to IGRA. This peak shows an EVPI of about NOK 39.4 per screened individual, which would be about NOK 630 000 if the estimate of the amount screened each year of 16 000 people is used.

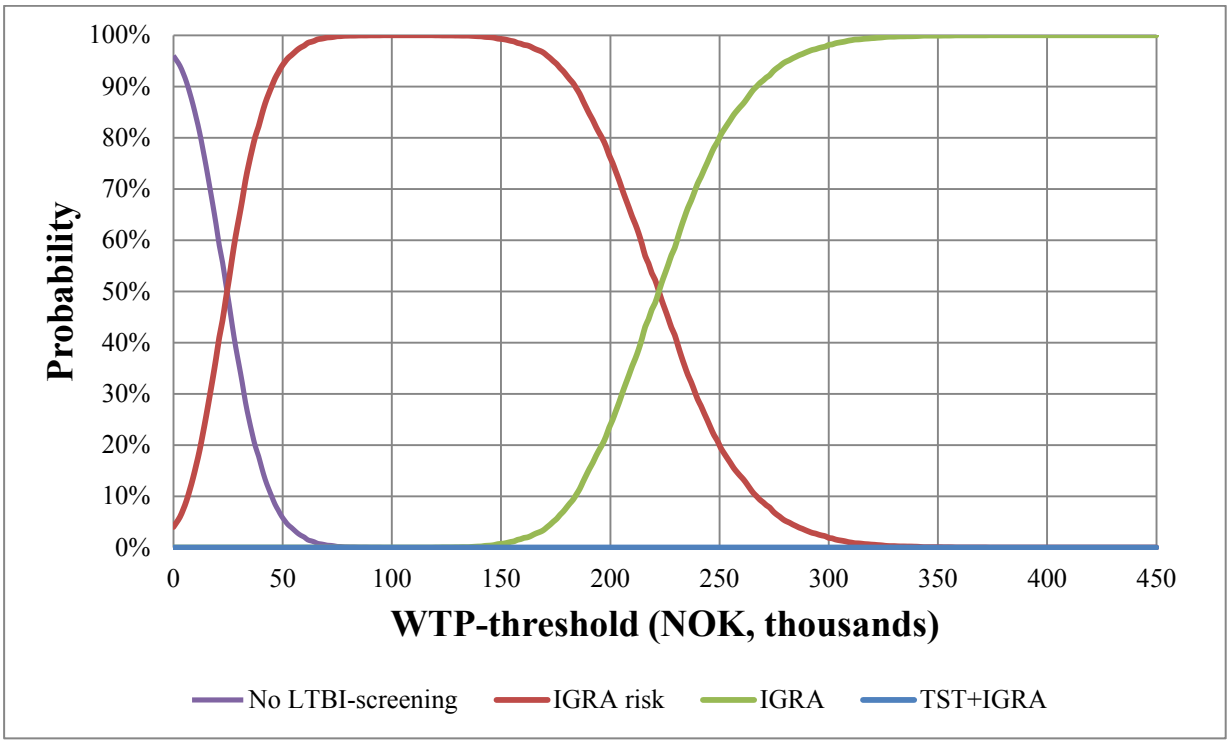

Figure 5 Cost-effectiveness acceptability curve

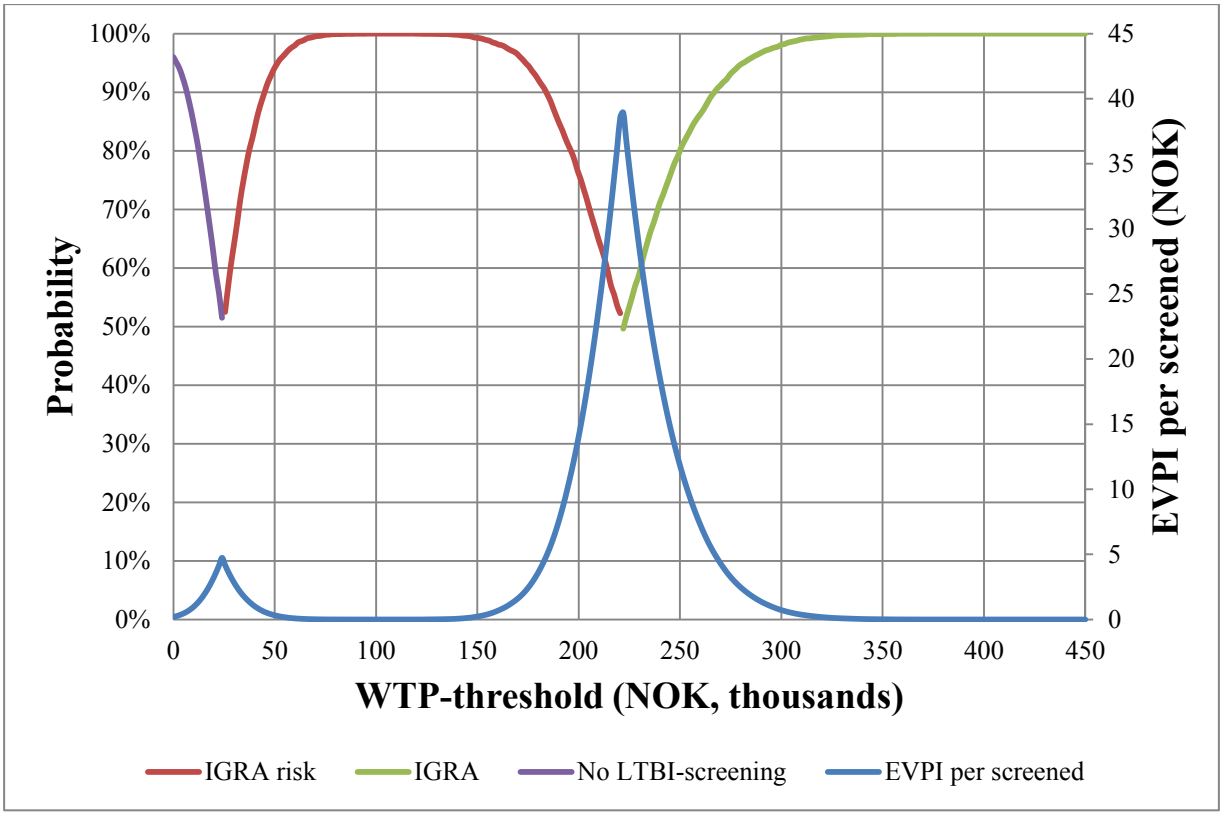

Figure 6 Cost-effectiveness acceptability frontier and expected value of perfect information curve

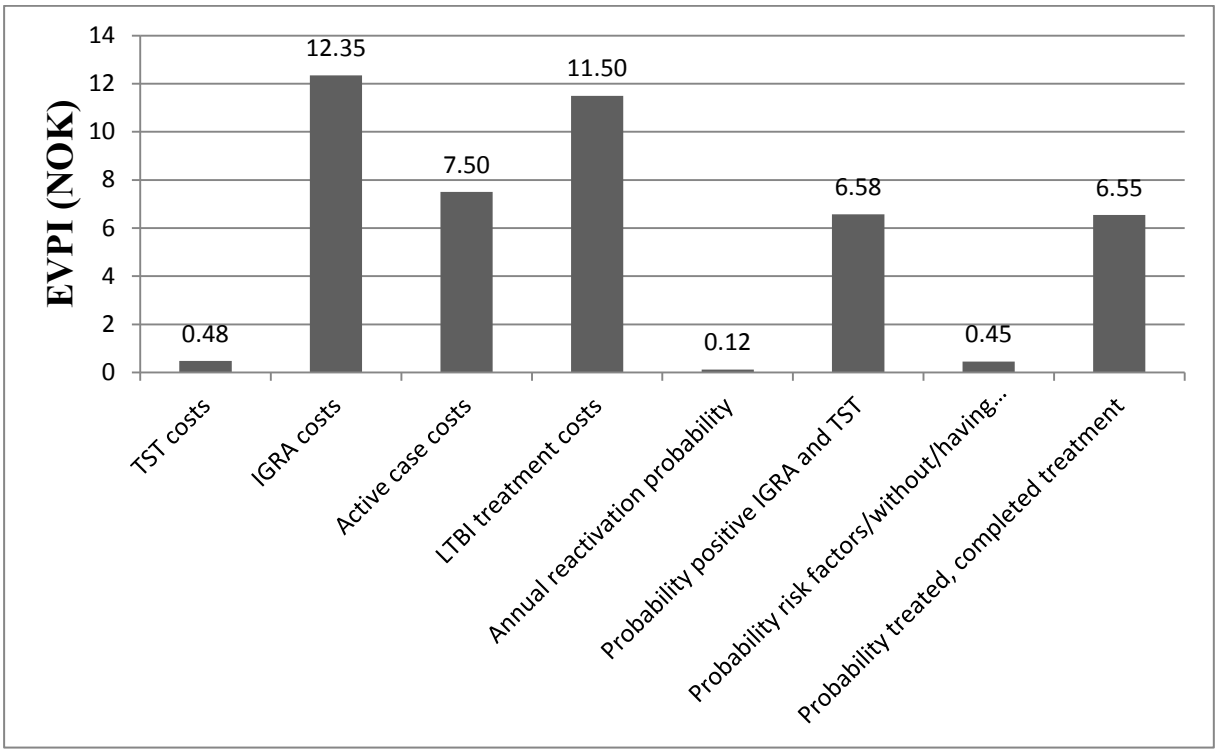

Figure 7 Expected value of perfect parameter information for costs and probabilities per screened individual.

In Figure 7 the expected value of perfect parameter information is plotted for groups of parameters. EVPPI was esimated at the WTP-threshold that caused the highest peak in EVPI (NOK 222 000) with 1000 inner and 1000 outer loops per group of parameters. The results for the other peak, NOK 24 000, are shown in Appendix VIII.

The results show that costs seem to be important parameters to focus further research on, especially the costs of IGRA and LTBI-treatment. If we assume 16 000 screened immigrants, the IGRA costs alone amount to an EVPPI of NOK 197 600. For the smaller peak at a WTP of NOK 24 000 active case costs had the highest potential gains from further reasearch (Appendix VIII). Here it should be mentioned again that the costs in this model were only point estimates which have been assigned a gamma distribution with a standard deviation of 10% of the point estimate. The information that comes from EVPPI for costs may then be limited.

It seemed as if the probabilities of having positive IGRAs and TSTs, and the probability of being treated and completing treatment were the most important probability parameters to research further. The least important group of parameters seemed to be the annual reactivation probabilities, although individual parameters may be low within other groups of parameters as well.

7 Discussion

7.1 General

The results of the model indicate that the TST+IGRA strategy is not cost-effective at any WTP-threshold, while the other strategies were cost-effective at different levels of the threshold. Ranging from least expensive and least effective to most expensive and most effective are no LTBI-screening, IGRA risk, TST+IGRA and IGRA.

If this study is used as a basis for making decisions, it should be decided how high the willingness to pay for an avoided case of TB is. It should be taken into account that these are costs in addition to the screening for and treatment of active TB. The limitations of this study and the results of other similar studies should also be taken into consideration. Many of the limitations of the study were taken into account in the sensitivity analysis, but some strengths and limitations will be discussed in the following sections.

7.2 Strengths and limitations

7.2.1 Probabilities

Sources of probabilities

One of the strengths of this study is that the sources used for most probabilities were based on Norwegian data. The results may provide information that is of use in a Norwegian setting, and estimates that can be of use in future Norwegian studies.

Whether the studies used as a source for many of the probabilities were representative could be discussed. The data from Winje et al. (2008) for instance, are based on asylum seekers from one relatively small time period. Immigrants who are not asylum seekers could have different IGRA and TST results than the ones in the study. In addition, which countries the immigrants originate in, and hence the prevalence of LTBI, will likely differ from time period to time period. Ideally RCTs or meta-analyses should be used to establish the probability of a positive or negative TST given a positive or a negative IGRA. Still, the results of the

sensitivity analysis indicate that varying these parameters did not influence which strategies were cost-effective. It did, however, affect the costs and effects of the strategies.

The sources of some probabilities, such as the probability of a screened individual going missing after undergoing TST and the probability of being HIV-infected were only expert opinion. However, it was hoped that the sensitivity analysis was robust enough to show that these probabilities did not influence the results substantially.

Reactivation probability and active cases

The annual reactivation probability used in this study was high compared to many other studies, at 1.1% and 3.2% of the low and high risk group respectively. A systematic review by Oxlade, Pinto, Trajman & Menzies (2013) looked at 14 different CEAs, of which only 3 used an annual reactivation probability over 1%. An often used estimate is that 5 to 10% of people with true LTBI reactivate during their *lifetime*, while my model resulted in 8.2% of the group without risk factors and 21.6% in the group with risk factors reactivating within 10 years. In addition some of those with negative tests reactivated as well. The high annual reactivation probabilities were probably due to two issues:

- The reactivation probability for the group without risk factors was actually based on data that also contained studies where people with risk factors were included. Since in my study the group without risk factors actually contains young children and recently infected it may be argued that this weakness is not substantial.
- Reactivation probability was extrapolated to 10 years when the follow-up was about 2 years. The high reactivation probability used in the meta-analysis may reflect a higher reactivation probability the first few years. The reduction in reactivation probability used in this study may not have been high enough to account for the real decline. In another study 10% decrease in risk each decade was used (Horsburgh, 2004), but this probability would likely still not be enough to make the active cases in line with other studies. It could be discussed whether it could be appropriate to have a follow-up of two years in my model instead since that is the approximate follow-up of the studies the meta-analysis is based on. Two years was considered to be too short given the nature of LTBI.

The result of the high reactivation probability is that the total amount of active cases of TB generated by this model is high compared to some other studies (Mulder, 2013; Pareek et al., 2011). For easier comparison, Appendix IV has a table with a cohort of 10 000, which is sometimes used in other studies looking at LTBI-screening. As shown in the sensitivity analysis, the relatively high amount of active cases caused the results to be more favorable to the strategies that involved screening for LTBI than would otherwise be the case.

My model used a somewhat different approach to dealing with LTBI in cost-effectiveness analyses than has been used earlier. Since there is no gold standard for determining whether a person has LTBI or not, it seems appropriate to base reactivation probability on the test's ability to predict reactivation instead of assuming an underlying prevalence of LTBI. Depending on what one's stance is on this issue, this approach could be considered one of the strengths of the study. One issue that will have to be dealt with when using this approach, which has not been dealt with here, is how to account for inconclusive IGRA-results.

Risk factors

Another strength of the study is that it takes into consideration people with risk factors. But several more risk factors could and arguably should have been considered. Young children, diabetics, people on immunosuppressant medication and people with end stage renal disease could all have been considered. Unfortunately the lack of time and data did not allow for it. Even if these risk factors were not included in the base analysis, it could be argued that the sensitivity analysis to some extent accounted for them since the probability of having risk factors was varied.

One problem in this study is that it may not be possible to know both the risk factors before choosing to screen, something that at least applies for HIV. In that case screening only people with risk factors could be implausible. However, it is likely possible to know the results of chest x-rays beforehand, and chest x-rays constitute the biggest part of the group with risk factors. In addition, other risk factors could plausibly be substituted for the HIV positive status used in this paper.

Two probability parameters in the group with risk factors should be discussed. First, as mentioned in the sensitivity analysis it could be argued that those who are in the group with risk factors are more likely to have a positive IGRA test. Ideally there should have been

separate estimates for the group with and the group without risk factors, but it was not possible to obtain data that allowed for it. For the same reason the probability of being put on treatment in the group with risk factors was the same as in the group without. Arguably this is unrealistic, and the estimate should have been higher for the risk group. The reason this may be unrealistic is that risk factors are supposed to be taken into account when deciding to treat (NIPH, 2013). As seen in the sensitivity analysis, if the probability of being treated increased to 50% for the high risk group, the IGRA risk strategy had less costs and more effects than no LTBI-screening. 50% probability of being treated in the risk group does not seem unrealistic.

The results of EVPPI suggest that obtaining better evidence on the probability of a positive IGRA or TST, the probability of being treated and treatment completion could yield benefits when deciding on which strategy is the cost-effective one between IGRA risk and IGRA. Further research should be conducted to get better estimates of these parameters.

Treatment completion

A simplification made in the model was that all individuals partially completing treatment could still develop active TB, and all individuals fully completing treatment had no probability of reactivation. Efficacy estimates for full LTBI treatment used in other studies range from 65% to 90% (Oxlade et al., 2013). My hope was that since incomplete treatment sometimes cures the infection and completed treatment sometimes does not, these would to some degree cancel each other out. Most likely however, the amount of people who are considered free of LTBI after treatment was overestimated in this study, probably causing the study to be more favorable towards the strategies that involved LTBI-screening.

Side effects of medication could also have been included because it could influence both treatment completion and costs of treating side effects such as drug induced liver injury. It was assumed that that those who stop treatment because of side effects were already part of the probability of completing treatment. The costs of treating side effects were not taken into account, and including them would probably make the results less favorable towards the strategies that involved the most treatment.

7.2.2 Costs

In general, the costs in this study may have been a weak link since they were only "typical case" estimates for the treatment costs. However, significant effort was put into estimating the costs as accurately as possible with help from people in many parts of the health system who are knowledgeable about the treatment of TB in Norway. In this section some points about the costs will be discussed.

Some costs do not include overhead costs. The IGRA and TST tests for instance, were composed of reimbursement rates (which include overhead) and time estimates (which do not). Including overhead costs would increase the costs of these tests, and overhead costs may be important. As seen in the sensitivity analysis, the cost of the TST in particular would have an influence on the additional costs of adopting the IGRA strategy.

The study did not take into account where the costs occur in the health system, something that could influence the results. For instance, it has been argued that replacing TST+IGRA with IGRA would result in freed resources at the asylum center, but an increased burden on the laboratories. If the freed resources at the asylum center would more than offset the increased costs at the laboratories, then the IGRA strategy would be viewed as more attractive.

In general reimbursement rates were used to a large extent in this study. These are not accurate estimates of the true costs. As suggested from the EVPPI and sensitivity analysis, better estimates of costs would increase the probability of correct decisions being made. The cost parameters were not based on patient level data, and because of that using EVPPI may not be completely justified. Still, EVPPI together with the different sensitivity analyses suggest that these are indeed parameters that it is important to gain more knowledge about.

One particularly weak cost estimate is that of hospitalization based on DRG. Some have criticized the DRG reimbursement for not covering the full costs (personal communication). However, the cost estimates for treating active TB in this study were higher than estimates made for instance in the Netherlands and Canada (Dasgupta et al., 2000; de Vries G & R, 2013). There are currently estimates being made on what the cost of a day in isolate costs in Norway, and these should be applied when making further analyses as they will probably be more accurate. It was hoped that the sensitivity analysis to some extent covered the uncertainty regarding this part of the costs.

Excluded costs

The cost of treating MDR-TB was not included in the study. This type of TB requires more expensive medication, longer treatment, and more tests. Excluding MDR-TB may lead to an underestimation of the treatment costs of active TB. To some extent the possible underestimation was accounted for in the sensitivity analysis by increasing the costs of treating active TB.

Another type of cost that was not included was patient transportation cost. Patient transportation costs were not included because it was difficult to obtain data. These costs are likely important because screening and treatment involves several trips back and forth from hospitals and these costs need to be covered by the health system. If these costs were included they would increase the costs of all strategies that involve screening. Because of the extra consultation used to take the TST, the cost of this test would increase more than the increase for IGRA. However, the IGRA strategy results in more people getting treated and because of that the costs of the IGRA strategy may have increased more than that of the TST+IGRA strategy.

The costs of contact tracing were not included. Every time a new active case surfaces an investigation has to be conducted where people are called in for screening. Costs are then incurred both at the NIPH and in primary health care for time used, and in addition there are the costs of the additional screening tests used. Including contact tracing would cause the IGRA strategy, which resulted in the most people treated, to be more attractive since fewer active cases would occur in the future. Generally the strategies that involved screening would have more favorable results.

The time used by TB-coordinators was to a large extent also excluded in the study, although not in the treatment plan meeting. If these costs were included, it would perhaps make the costs of TST+IGRA and IGRA increase more than IGRA risk since those two strategies involve more work for the TB-coordinator because more people are screened and treated.

7.2.3 Other issues in the model

Because of time limitations QALYs were not used in this study. As a result it is not possible to compare the interventions in this study to other health-care interventions. One benefit to using avoided cases is that this is unambiguously the goal of a LTBI-screening program. The

outcome used in other cost-effectiveness analyses looking at LTBI-screening varies, and both QALYs and avoided cases of active TB have been used. Ideally both should have been used in this study. Focus of further research using this model should perhaps be focused on implementing QALYs.

Discounting of effects was not done in the base study because it was decided that the amount of avoided cases was an interesting number in itself. Discounting would cause the number of avoided cases to be difficult to interpret. Not discounting effects could be considered a weakness since the Directorate of Health recommends discounting both costs and effects. However, discounting of effects was done as an alternative and those results may be referred to if needed.

The comparator used in this analysis was no screening for LTBI instead of the current strategy. No screening was used as a comparator because avoided cases of active TB was the outcome, meaning that the strategies would already have to be compared to no screening on the effect side. It was also thought that since the strategy would likely be changed, using no screening as a comparator would keep the analysis more open for later use. This choice of comparator may make it more difficult to see the consequences of moving from TST+IGRA to another strategy, but effort has been put into explaining and displaying results that illustrate these consequences.

The study could have been more detailed in modelling screening for active TB and treatment of active TB. In the model it was assumed that all people with active TB would be detected, and all received and accepted treatment. All of them also completed treatment, were cleared of TB and could no longer be infected. In addition, there was no probability that people with active TB could infect others in the main results. When secondary cases of active TB were accounted for, there was still no possibility of infecting others with LTBI or for the disease to spread further from those who got infected. Being more detailed in this matter would probably lead the strategies that involved LTBI-screening to be less attractive (higher ICERs).

It could be discussed whether background mortality should be added to this model, but it was thought that it would only have a small impact since the time horizon was 10 years. Mortality from TB was not included either, but the number of deaths from TB is very small in a developed country like Norway and the impact would be small.

One issue that was not discussed in the model was how a change in strategy would influence the amount of people who take the tests. In my model it was assumed that all immigrants from countries with a high prevalence of TB took the screening tests. In reality, getting everyone to take the tests may not be as easy. One benefit of only screening with IGRA could potentially be that it would be easier to get the immigrants to take the test because they would know that the process is shorter. To some extent this was taken into account because it was possible for the immigrants to disappear after a TST.

Moving from TST+IGRA to IGRA would according to this model approximately cost an additional NOK 2.5 million. When pharmaceutical companies in Norway apply for reimbursement for a drug, the Norwegian Medicines Agency has a limit of NOK 5 million in additional resources spent before the decision to reimburse has to go to the Ministry of Health and Care services (Norwegian Medicines Agency, 2014a). This is because NOK 5 million is considered to be a relatively low sum. If we use this as a reference when looking at these screening strategies then an additional NOK 2.5 million may not be considered a substantial amount of extra resources spent.

7.3 Findings of other studies

Studies that have compared similar strategies to the ones compared here have reached varying conclusions.

A systematic review found that of the six studies comparing TST+IGRA to IGRA alone, four of them found TST+IGRA the cost-effective alternative, while the other two found IGRA alone to be cost-effective (Nienhaus, Schablon, Costa, & Diel, 2011). A study by Mulder et al. comparing no screening, TST+IGRA and IGRA found TST+IGRA to be the cost-effective alternative in the Netherlands (Mulder, 2013). A study by Linas, Wong, Freedberg & Horsburgh (2011) comparing no screening, TST-screening and IGRA-screening found IGRA screening to be the cost-effective strategy when screening groups of people with risk factors. TST only was never a relevant strategy in my study, but it is relevant to see that IGRA was cost-effective compared to no screening. One study concluded IGRA only to be the "cost-effective" option when used on foreign-born population, but the study only looked for cost savings (Iqbal et al., 2014).

A study by Pareek et al. (2011) also found screening with IGRA to be cost-effective compared to no-screening when the incidence in the country of origin was high enough. When screening immigrants who came to the UK between the ages of 16 and 35 from a country with an incidence of TB above 250 per 100 000 population, about 30% had positive IGRAs. We do not know the combined incidence in countries of origin of the immigrants who come to Norway, but the proportion of positive IGRAs in my study was about 29% which should make the two comparable. In the study by Pareek et al. the ICER was £17 956 in 2010 pounds per avoided case of TB when screening with IGRA only (Pareek et al., 2011). This would be about NOK 190 000 in 2013 prices. The ICER for IGRA in my study was about NOK 221 000, which is a comparable number.

It seems like other studies provide different conclusions as to which of the strategies IGRA and TST+IGRA are the most cost-effective, but there seems to be a general agreement that screening for LTBI is cost-effective.

8 Conclusion and policy implications

The results of the model indicate that no screening for LTBI, screening only immigrants at risk for reactivation with IGRA and screening all immigrants with IGRA were cost-effective at different thresholds of willingness to pay (WTP). In this model screening with TST and IGRA was not cost-effective at any WTP-thresholds.

Based on the results of the cost-effectiveness acceptability frontier, no screening for LTBI had the highest expected net benefit if WTP was NOK 24 000 or below. Between a WTP of NOK 24 000 up to NOK 222 000 screening only immigrants with risk factors had the highest expected net benefit. From NOK 222 000 and up screening all immigrants with IGRA had the highest expected net benefit. The additional costs of adopting the IGRA-strategy from TST and IGRA were NOK 2.5 million for a cohort of 16 000, and would avoid 18.5 more cases over 10 years. The additional costs were sensitive to the cost of the TST. The model indicates that adopting the IGRA-risk strategy would reduce costs by NOK 8.5 million compared to TST+IGRA, but avoid 31 fewer cases. The no LTBI-screening strategy would cost about NOK 300 000 less than the IGRA-risk strategy. As shown by the cost-effectiveness acceptability curve there is a relatively high probability of making the wrong decision if WTP is around NOK 222 000 or NOK 24 000. More effort should be put into further research on the costs of TB. This can potentially have high returns, as can be seen from the expected value of perfect information and sensitivity analysis.

The policy implications are these: Should *more* money be spent and increase the amount of avoided cases (going for the IGRA-strategy), or should *less* money be spent and avoid fewer cases by either adopting the IGRA risk-strategy or the no-screening strategy? This depends on the decided WTP. Either way, the results of the model indicate that the TST and IGRA strategy should be discarded. However, the results of some other analyses in other countries have shown TST and IGRA to be cost-effective and these results should also be taken into consideration.

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Appendix I: Decision trees

All decision trees were developed using Simple Decision Tree for Excel. The rightmost part of each decision tree indicates the Markov starting states that each branch leads to.

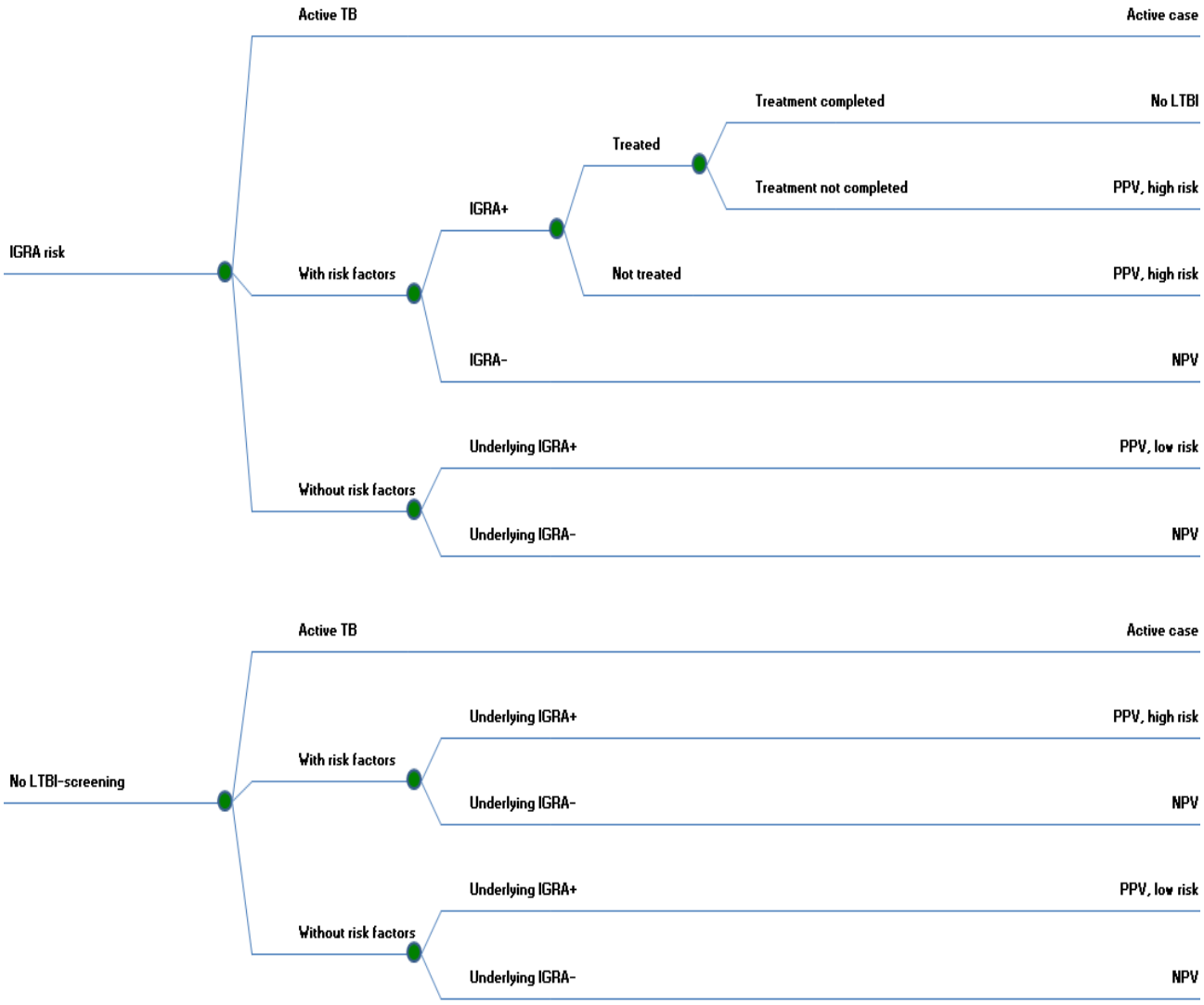

Figure I and II Decision trees for No LTBI-screening and IGRA risk

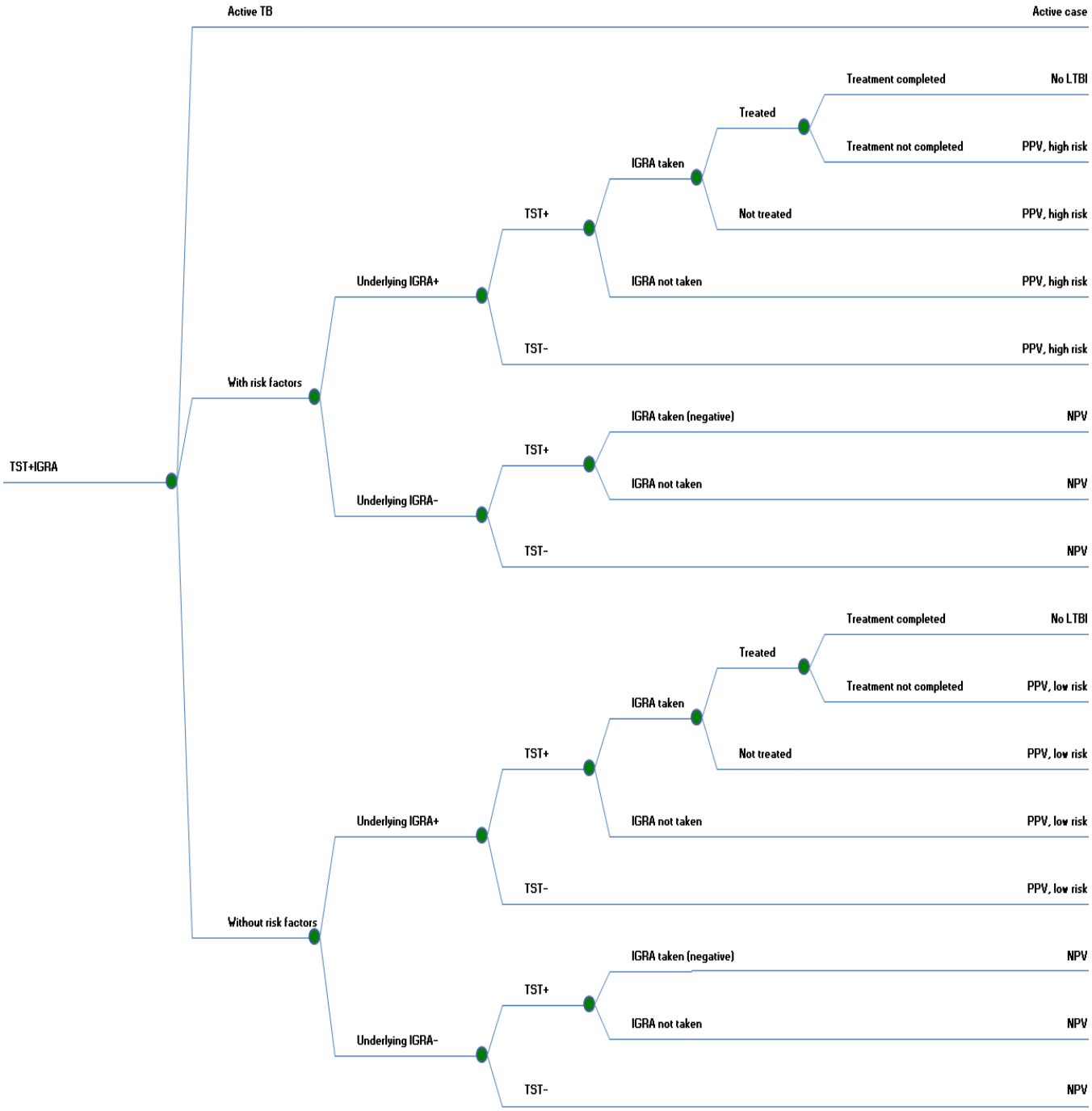

Figure III Decision tree for TST+IGRA

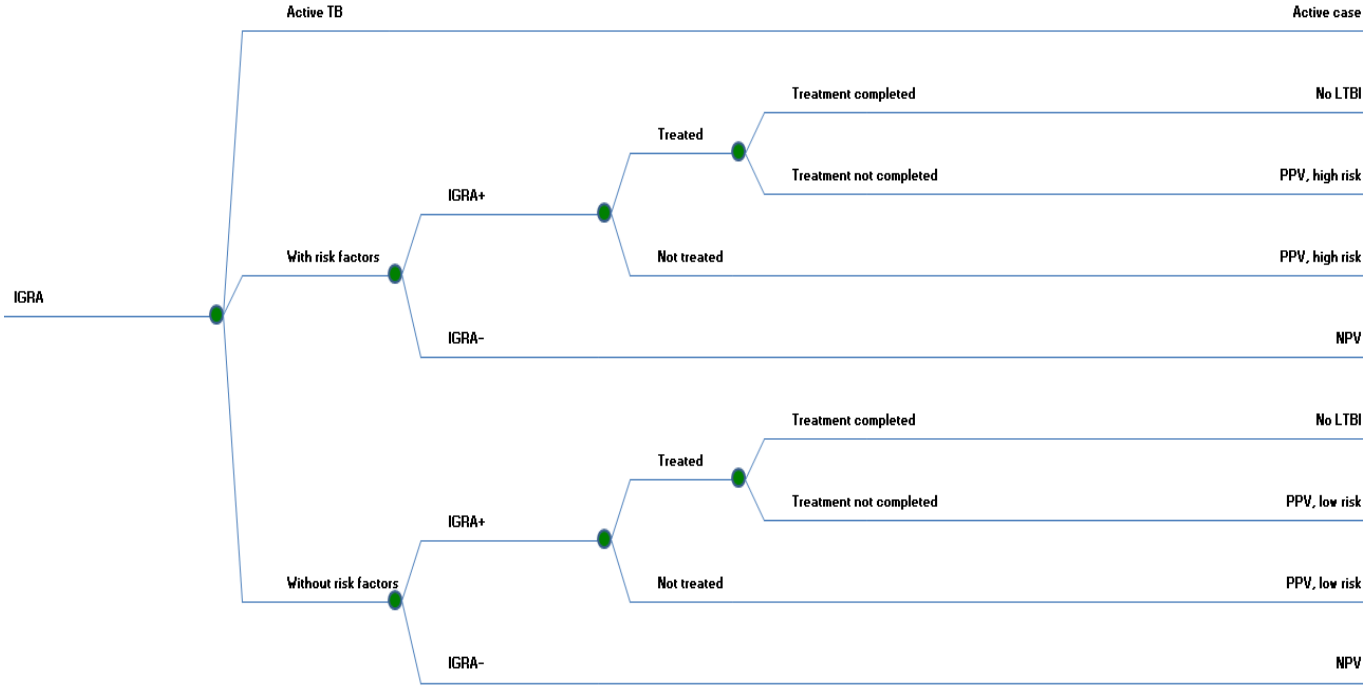

Figure IV Decision tree for IGRA

Appendix II: Costs

All costs taken from fee schedules or other reimbursement rates (except DRG) are multiplied by 2 to obtain a closer approximation to full costs. Wages found at Statistics Norway are multiplied by 1.4 to obtain an approximation to full cost (payroll tax, national insurance scheme).

Table I Table showing detailed costs

		Source(s)
Screening costs		
IGRA		
Time for taking test (minutes)	15	Time estimate acquired from personal communication with Oslo Municipality and Stavanger University Hospital
Wage per hour (NOK)	318.8	(Statistics Norway, 2013)
Labor costs for taking test (NOK)	79.7	Wage per hour*time
Analysis (NOK)	306	Reimbursement category 703U and 704L times 3 (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Categories given by Department of Microbiology, Oslo University Hospital. Includes cost for IGRA-kit
Total (NOK)	**386**	
TST		
Time (minutes)	30	Time estimate acquired by personal communication with Oslo Municipality and NIPH
Wage per hour (NOK)	318.8	(Statistics Norway, 2013)
Labor costs for taking test (NOK)	159.4	Wage per hour*time
Tuberculin (NOK)	126.8	(NIPH, 2014)
Proportion used for one test	1/15	(NIPH, 2013)
Costs of tuberculin used each test (NOK)	8.5	Tuberculin costs*proportion used each test
Total (NOK)	**168**	
Chest x-ray		
Reimbursement rate (NOK)	56	(Forskrift om dekning av laboratorieutgifter, 2013)
Patient user charge (NOK)	448	(Forskrift om dekning av laboratorieutgifter, 2013)
Total (NOK)	**504**	Chest x-rays taken during treatment are assumed to be covered by DRG for follow-up consultations

HIV-test

Costs of taking test (NOK)	96	Fee schedule category 701A (Norwegian Medical Association, 2013)
Analysis (NOK)	50	Reimbursement category 704N (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Category given by Oslo University Hospital
Total (NOK)	**146**	

Treatment costs

Laboratory tests

Sputum smear costs (NOK)	**106.3**	Wage rate*time used (20 minutes). Estimate by Oslo University Hospital
Quantity pulmonary TB	1	Rest covered by DRG
Quantity extra-pulmonary TB	1	Rest covered by DRG
Quantity latent TB	1	
Direct microscopy (NOK)	**42**	Reimbursement category 704B (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Category given by Levanger Hospital.
Quantity pulmonary TB	3	
Quantity extra-pulmonary TB	3	
Quantity latent TB	1	
Resistance determination (NOK)	**260**	Reimbursement category 704Cx5 (Forskrift om utgifter til poliklinisk helsehjelp, 2013) Category given by Oslo University Hospital.
Quantity pulmonary TB	1	
Quantity extra-pulmonary TB	1	
Quantity latent TB	0	
PCR (NOK)	**704**	Reimbursement categories 701B+701C+701G (Forskrift om utgifter til poliklinisk helsehjelp, 2013) Categories given by Oslo University Hospital.
Quantity pulmonary TB	2	
Quantity extra-pulmonary TB	2	
Quantity latent TB	0	
Culture (NOK)	**52**	Reimbursement category 704C (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Category given by Oslo University Hospital.
Quantity pulmonary TB	7	
Quantity extra-pulmonary TB	7	
Quantity latent TB	3	

Identification (NOK)	**772**	Reimbursement categories 701B+701C+701D+701G (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Categories given by Oslo University Hospital.
Quantity pulmonary TB	1	
Quantity extra-pulmonary TB	1	
Quantity latent TB	0	
Blood tests		
Costs of taking test (NOK)	96	Fee schedule category 701A (Norwegian Medical Association, 2013).
Types of analyses		
CRP (NOK)	24	Reimbursement category 707B (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Category given by Oslo University Hospital.
Other types of analyses (NOK)	72	Reimbursement category 704A*9 types of analyses (Forskrift om utgifter til poliklinisk helsehjelp, 2013). Category given by Oslo University Hospital.
Total (NOK)	**192**	
Quantity pulmonary TB	1	One that is not covered by DRG for follow-up consultations
Quantity extra-pulmonary TB	1	One that is not covered by DRG for follow-up consultations
Quantity latent TB	1	One that is not covered by DRG for follow-up consultations
Treatment plan meeting		
Length of meeting (minutes)	60	Expert opinion at NIPH.
Wage, doctor (NOK)	565.2	(Statistics Norway, 2013)
Wage, TB-coordinator (NOK)	318.8	(Statistics Norway, 2013)
Wage, home services (NOK)	318.8	(Statistics Norway, 2013)
Wage, community nurse (NOK)	318.8	(Statistics Norway, 2013)
Total (NOK)	**1521.5**	
Quantity pulmonary TB	1	
Quantity extra-pulmonary TB	1	
Quantity latent TB	1	

Hospitalization		
Value of one DRG point (NOK)	39447	(The Norwegian Directorate of Health, 2012a)
Weight given for TB	2.696	DRG 79. Category given by the Norwegian Directorate of Health
Total (NOK)	**106349**	39447*2.696
Quantity pulmonary TB	1	
Quantity extra-pulmonary TB	0	
Quantity latent TB	0	
Follow-up consultations		
Value of one DRG point (NOK)	39447	(The Norwegian Directorate of Health, 2012a)
Weight given for TB follow-up	0.043	DRG 904D. Category given by the Norwegian Directorate of Health
Total (NOK)	**1696**	
Quantity pulmonary TB	4	
Quantity extra-pulmonary TB	4	
Quantity latent TB	2	
Nurse home visits		
Wage, weekday (per hour, NOK)	489	Personal communication UNICARE, Oslo Municipality
Wage, weekend (per hour,NOK)	699	Personal communication UNICARE, Oslo Municipality
Extra charge per visit (NOK)	56	Personal communication UNICARE, Oslo Municipality
Esimated time spent per visit (minutes)	10	Personal communication UNICARE
Weight given to weekday	5/7	
Weight given to weekend	2/7	
Total, one visit (NOK)	**147.5**	((489*10 minutes)*5/7)+((699*10 minutes)*2/7)+56
Quantity pulmonary TB	166	
Quantity extra-pulmonary TB	180	
Quantity latent TB	90	Only used in about 52% of treatments (see Table 1)
Interpreter		
Hourly wage (NOK)	**844**	Average hourly wage paid by Oslo University Hospital
Quantity pulmonary TB	8	Estimated based on number of patients and total hours used at Oslo University Hospital
Quantity extra-pulmonary TB	8	Estimated based on number of patients and total hours used at Oslo University Hospital
Quantity latent TB	2	Assumed

Medication		
Isoniazid+rifampicin (Rimactazid)		(Follow-up phase and LTBI)
Maximum pharmacy purchase price (NOK)	188.9	(Norwegian Medicines Agency, 2014b)
Amount of tablets in box	60	(Norwegian Medicines Agency, 2014b)
Amount of tablets to be taken each day	4	Assumed a person of 70kg weight. Amount of tablets per kilo taken from (NIPH, 2013).
Cost per daily dose (NOK)	**12.6**	(188.9/60)*4
Quantity pulmonary TB	120	(NIPH, 2013)
Quantity extra-pulmonary TB	120	(NIPH, 2013)
Quantity latent TB	90	(NIPH, 2013)
Isoniazid+rifampicin+pyrazinamid+ ethambuthol (Rimstar)		(Intensive phase)
Maximum pharmacy purchase price	478.4	(Norwegian Medicines Agency, 2014b)
Amount of tablets in box	60	(Norwegian Medicines Agency, 2014b)
Amount of tablets to be taken each day	4	Assumed a person of 70kg weight. Amount of tablets per kilo taken from (NIPH, 2013).
Cost per daily dose	**31.9**	(478.4/60)*4
Quantity pulmonary TB	46	(NIPH, 2013)
Quantity extra-pulmonary TB	60	(NIPH, 2013)
Quantity latent TB	0	(NIPH, 2013)

Appendix III: Cost-effectiveness plane

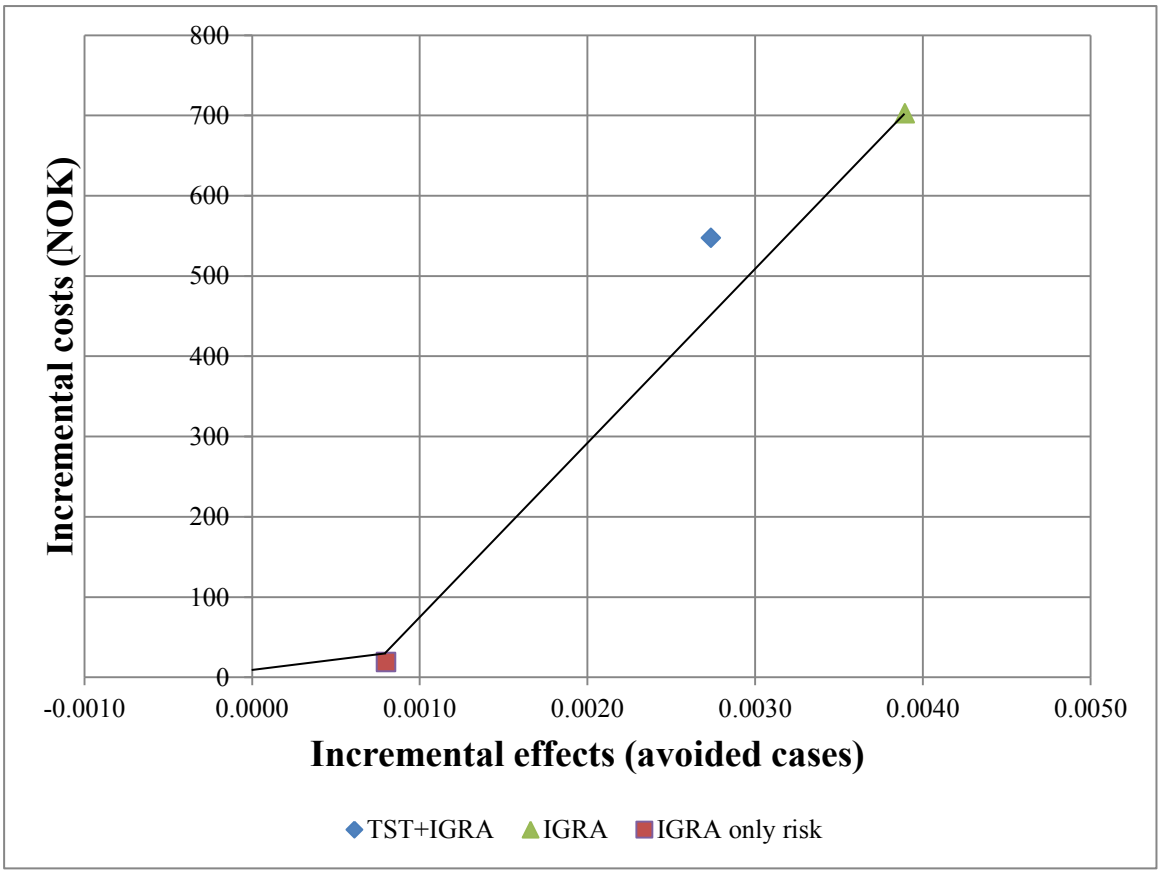

Figure V Cost-effectiveness plane

Appendix IV: Alternative display of results

Table II Results with a cohort of 10 000

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	47 557 157	0	399,9	Baseline	Baseline	Baseline
IGRA risk	47 747 209	8,0	391,9	190 051	7,9990	23 760
TST+IGRA	53 031 994	27,4	372,6	Extended dominance	Extended dominance	Extended dominance
IGRA	54 585 556	38,9	361,0	6 838 348	30,9417	221 008

Table III Results when active cases are discounted at the same rate as costs (4%)

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	4 756	0	0.0342	Baseline	Baseline	Baseline
IGRA risk	4 775	0.0007	0.0335	19	0.0007	28 343
TST+IGRA	5 303	0.0023	0.0319	Extended dominance	Extended dominance	Extended dominance
IGRA	5 459	0.0033	0.0309	684	0.0026	265 110

Appendix V: Scenario analysis

Table IV Results without costs of treatment of active TB

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	621	0	0.0400	Baseline	Baseline	Baseline
IGRA risk	721	0.0008	0.0392	100	0.0008	125 119
TST+IGRA	1 445	0.0027	0.0373	Extended dominance	Extended dominance	Extended dominance
IGRA	1 717	0.0039	0.0361	996	0.0031	321 858

Table V Results when reactivation probabilities reduced in all groups (0.0025 and 0.0045 annual probability)

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	1 974	0	0.0126	Baseline	Baseline	Baseline
IGRA risk	2 058	0.0002	0.0125	84	0.0002	515 343
TST+IGRA	2 722	0.0008	0.0119	Extended dominance	Extended dominance	Extended dominance
IGRA	2 963	0.0011	0.0115	905	0.0009	975 299

Table VI Results with secondary cases (0.2 per reactivated case)

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	5 462	0	0.0470	Baseline	Baseline	Baseline
IGRA risk	5 465	0.0010	0.0460	3	0.0010	2 906
TST+IGRA	5 954	0.0033	0.0437	Extended dominance	Extended dominance	Extended dominance
IGRA	6 086	0.0047	0.0423	621	0.0037	167 365

Table VII Results when probability of group with risk factors being put on treatment is increased to 0.9

	Costs (NOK)	Avoided cases	Active cases	Incremental costs (NOK)	Incremental avoided cases	ICER (NOK)
No screening	4 756	0	0.0400	Baseline	Baseline	Baseline
IGRA risk	4 700	0.0042	0.0358	-56	0.0042	-13 137
TST+IGRA	5 251	0.0052	0.0348	Extended dominance	Extended dominance	Extended dominance
IGRA	5 384	0.0073	0.0327	684	0.0031	221 008

Appendix VI: One-way sensitivity analysis for probabilities

Table VIII Several one-way analyses for probabilities, with and without extendedly dominated (ED) strategies.

ICERs are relative to the strategy to its left. IGRA risk is compared to no-screening (not shown).

	Base esimate	Values explored	IGRA risk (ICER)	TST+IGRA (ICER)	IGRA (ICER)
Probability IGRA-positive (both groups)	0.29	0.1	109 951	ED	435 096
		0.2	44 110	ED	271 556
		0.3	22163	ED	217 043
		0.4	11 190	ED	189 787
		0.5	4606	ED	173 433
Extendedly dominated strategy included		0.1	109 951	508 850	311 511
		0.2	44 110	328 479	176 174
		0.3	22 163	268 356	131 062
		0.4	11 190	238 294	108 506
		0.5	4 606	220 257	94 972
Probability IGRA-positive, high risk group	0.29	0.29	23760	ED	221 008
		0.39	12034	ED	221 008
		0.49	5 143	ED	221 008
		0.59	589	ED	221 008
		0.69	-2646	ED	221 008
Extendedly dominated strategy included		0.29	23 677	272 798	134 278
		0.39	12 034	286 608	122 772
		0.49	5 143	301 697	112 696
		0.59	589	318 250	103 798
		0.69	-2 646	336 491	95 884
Probability of having risk factors	0.09	0.05	25 654	ED	221 008
		0.1	23 501	ED	221 008
		0.15	22 783	ED	221 008
		0.2	22 424	ED	221 008
		0.25	22 208	ED	221 008
Extendedly dominated strategy included		0.05	25 654	258 151	148 320
		0.1	23 501	277 248	130 790
		0.15	22 783	302 276	115 558
		0.2	22 424	336 505	102 199
		0.25	22 208	386 151	90 388
Probability treated (both groups)	0.17	0.1	55 610	ED	300 121
		0.3	4 050	ED	172 052
		0.5	-6 262	ED	146 438
		0.7	-10 682	ED	135 460
		0.9	-13 137	ED	129 362
Extendedly dominated strategy included		0.1	55 610	376 918	171 436
		0.3	4 050	208 254	111 389
		0.5	-6 262	174 521	99 379
		0.7	-10 682	160 064	94 232
		0.9	-13 137	152 033	91 373
Probability treated, high risk group	0.17	0.1	55 610	ED	221 008
		0.3	4 050	ED	221 008
		0.5	-6 262	ED	221 008
		0.7	-10 682	ED	221 008
		0.9	-13 137	ED	221 008

Extendedly dominated strategy included		0.1	55 610	258 577	148 766
		0.3	4 050	303 179	113 159
		0.5	-6 262	364 662	89 855
		0.7	-10 682	454 843	73 417
		0.9	-13 137	599 937	61 201
Probability of completing treatment	0.84	0.5	96 608	ED	407 763
		0.6	66 710	ED	331 116
		0.7	45 354	ED	276 369
		0.8	29 338	ED	235 308
		0.9	16 880	ED	203 372
Extendedly dominated strategy included		0.5	96 608	492 278	266 145
		0.6	66 710	402 172	212 052
		0.7	45 354	337 811	173 414
		0.8	29 338	289 540	144 435
		0.9	16 880	251 995	121 896
Annual reactivation probability, low risk group	0.011	0.0025	23 760	ED	1 312 588
		0.0075	23 760	ED	378 344
		0.0125	23 760	ED	191 463
		0.0175	23 760	ED	111 348
		0.0225	23 760	ED	66 822
Extendedly dominated strategy included		0.0025	23 760	2 706 764	507 961
		0.0075	23 760	490 777	217 384
		0.0125	23 760	234 666	116 852
		0.0175	23 760	135 592	65 851
		0.0225	23 760	82 999	35 000
Annual reactivation probability, high risk group	0.032	0.0035	ED	ED	242 603
		0.0045	ED	ED	239 693
		0.0075	ED	ED	231 363
		0.0100	ED	ED	224 845
		0.0200	89 989	ED	221 008
Extendedly dominated strategy included		0.0035	932 123	236 336	186 289
		0.0045	705 313	237 612	183 857
		0.0075	387 765	241 448	176 892
		0.0100	268 674	244 652	171 442
		0.0200	89 989	257 521	152 369
Decline in annual reactivation probability	0.081	0	-1 030	ED	148 401
		0.05	13 747	ED	191 734
		0.1	30 237	ED	239 913
		0.15	48 201	ED	292 226
		0.2	67 300	ED	347 661
Extendedly dominated strategy included		0	-1 030	187 341	82 684
		0.05	13 747	238 303	113 509
		0.1	30 237	294 960	147 801
		0.15	48 201	356 472	185 058
		0.2	67 300	421 647	224 562

The following strategies only affected the ICERs when the extendedly dominated strategy was included, hence these are only shown including that strategy.

	Base esimate	Values explored	IGRA risk (ICER)	TST+IGRA (ICER)	IGRA (ICER)
Probability of being missing following TST	0.2	0	23 760	237 556	129 077
		0.1	23 760	252 502	132 816
		0.2	23 760	272 728	134 343
		0.3	23 760	301 630	135 172
		0.4	23 760	346 314	135 693
Probability TST positive,	0.88	0.6	23 760	404 972	123 866
given (underlying) IGRA positive		0.7	23 760	338 402	126 402
		0.8	23 760	296 342	130 066
		0.9	23 760	267 359	135 823
		1	23 760	246 175	146 186
Probability TST positive,	0.35	0	23 760	233 087	200 767
given (underlying) IGRA negative		0.15	23 760	249 987	172 449
		0.3	23 760	266 886	144 131
		0.45	23 760	283 786	115 814
		0.6	23 760	300 685	87 496

Appendix VII: One-way sensitivity analysis for costs

Table IX Several one-way analyses for costs, with and without the extendedly dominated (ED) strategies included.

	Base esimate	Values explored	IGRA risk (ICER)	TST+IGRA (ICER)	IGRA (ICER)
Cost, treatment of active TB	120 946	75 000	62 265	ED	259 319
		125 000	20 362	ED	217 627
		175 000	-21 541	ED	175 935
		225 000	-63 444	ED	134 242
		275 000	-105 346	ED	92 550
Extendedly dominated strategy included	120 946	75 000	62 265	311 016	172 694
		125 000	20 362	269 350	130 958
		175 000	-21 541	227 683	89 223
		225 000	-63 444	186 017	47 487
		275 000	-105 346	144 350	5 752
Cost, treatment of latent TB	15 133	5 000	-31 897	ED	75 021
		10 000	-4 435	ED	147 053
		15 000	23 027	ED	219 086
		20 000	50 489	ED	291 118
		25 000	77 951	ED	363 151
Extendedly dominated strategy included	15 133	5 000	-31 897	115 668	6 911
		10 000	-4 435	193 164	69 788
		15 000	23 027	270 661	132 665
		20 000	50 489	348 157	195 542
		25 000	77 951	425 653	258 419
Cost, IGRA	386	300	13 624	ED	195 834
		350	19 517	ED	210 470
		400	25 409	ED	225 106
		450	31 302	ED	239 742
		500	37 194	ED	254 378
	386	300	13 624	258 871	90 205
		350	19 517	266 928	115 866
		400	25 409	274 984	141 528
		450	31 302	283 040	167 189
		500	37 194	291 097	192 851
Cost, TST	168	100	23 760	ED	221 008
		175	23 760	ED	221 008
		250	23 760	ED	221 008
		325	23 760	ED	221 008
		400	23 760	ED	221 008
Extendedly dominated strategy included	168	100	23 760	237 724	192 998
		175	23 760	276 428	128 142
		250	23 760	315 133	63 287
		325	23 760	353 838	-1 568
		400	23 760	392 542	-66 424

Appendix VIII: EVPPI

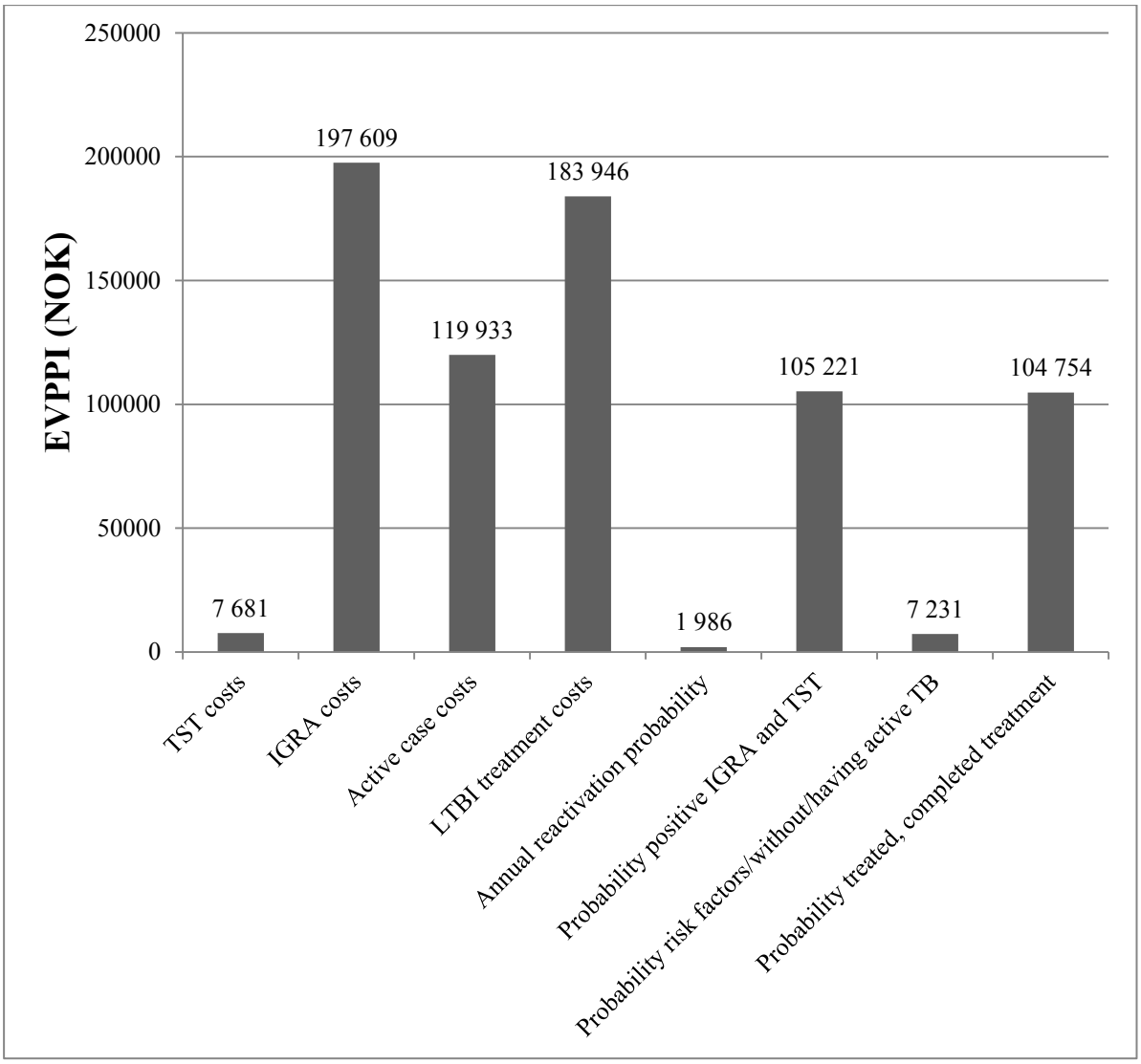

Figure VI Showing results of EVPPI for a cohort of 16 000 at a WTP-threshold of 222 000 NOK.

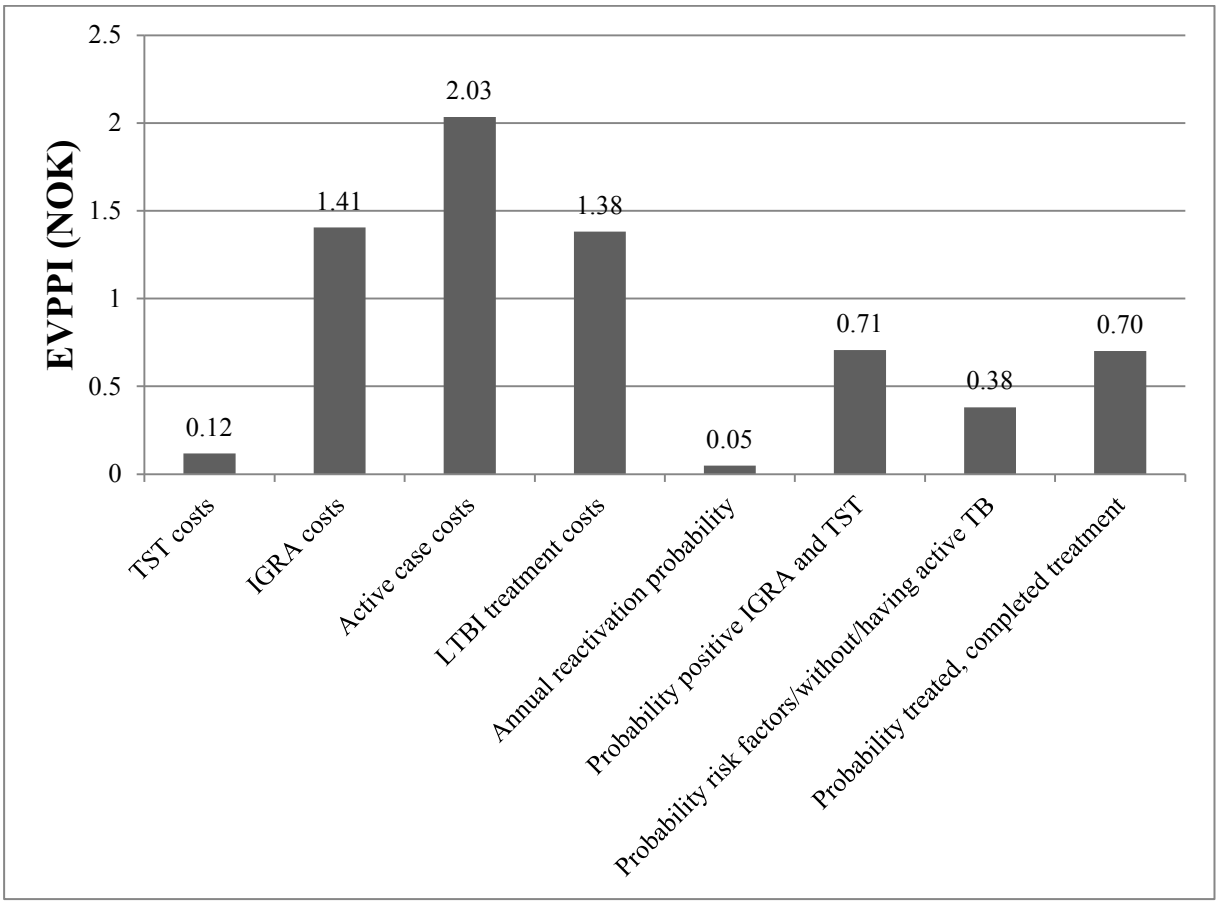

Figure VII Figure showing the results of EVPPI at a threshold of 24 000 NOK per screened individual.

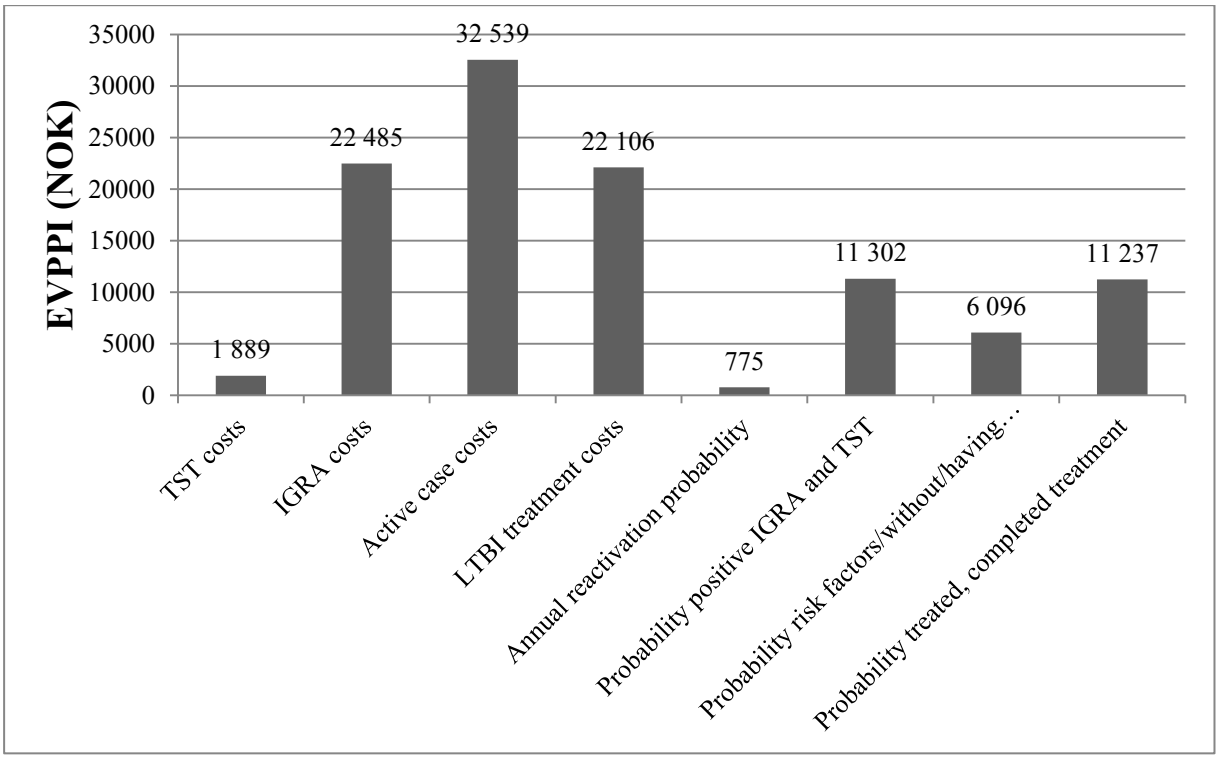

Figure VIII Figure showing results of EVPPI at a threshold of 24 000 NOK for a cohort of 16 000